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EXAMINING NEUROBEHAVIORAL EFFECTS OF CHEMOSENSORY EXPOSURE TO LOCAL IRRITANTS USING EVENT RELATED POTENTIALS

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ABSTRACT

The aim of this thesis was to examine whether unpleasant odors disturb cognitive task performance. At first glance, it seems intuitive that for example the smell of fire smoke would immediately interrupt my current writing at the computer. However, the same aim has been addressed in earlier investigations but outcomes were inconsistent, some reporting improvement by odors, some impairment. The basic assumption of this thesis is that former inconsistencies were due to the use of different odorants, the use of different tasks, or the general weakness of examining only behavioral performance.

The empirical studies performed for this thesis improved all three points: First, by comparing performance during inhalation of three different concentrations (low, middle, high) of one odorant in the same individual (human volunteers), second, by choice of a task that was assumed especially sensitivity for olfactory distraction and third, by measuring brain activation in addition to behavioral performance. All studies were performed with a special focus on workplace relevance, since unpleasant odors likely occur at industrial workplaces and distraction from demanding work tasks could endanger workers' health.

Three substances with workplace relevance were selected. Cyclohexylamine showed strongest and most unpleasant chemosensory effects and was therefore expected to cause stronger distraction than the moderate propionic acid. The neurotoxin ethyl acetate was examined for subtle indication of neurotoxicity. Performance in the cognitive task of response inhibition, which has been shown to interfere with emotional context, was observed on the behavioral (accuracy and speed) and brain level. Encephalography (EEG) was recorded, and well-described EEG curve components were analyzed, which were known to represent response inhibition.

Despite controlled study design and task selection the three studies did not present consistent results. Only propionic acid exposure evoked behavioral and EEG findings that both indicated exposure related impairment of response inhibition. The other assumptions could not be confirmed. One new finding was, that exposure to varying (but lower) exposure levels caused a distinct modulation of the EEG curve. This implicated that olfactory mediated distraction might be determined by other characteristics than odorant intensity or pleasantness.

It can be concluded that EEG implementation to occupational human inhalation exposures was successful and that the method could help to advance understanding of the field.

LIST OF PUBLICATIONS

I. Hey K, Juran S, Schäper M, Kleinbeck S, Kiesswetter E, Blaszkewicz M, Golka K, Brüning T, van Thriel C (2009). **Neurobehavioral effects during exposures to propionic acid - An indicator of chemosensory distraction?** *NeuroToxicology, 30, 1223-1232*.

II. Juran S, van Thriel C, Kleinbeck S, Schäper M, Falkenstein M, Iregren A, Johanson G (2009) **Neurobehavioral performance in human volunteers during inhalation exposure to the unpleasant local irritant cyclohexylamine**. *NeuroToxicology, http://dx.doi.org/10.1016/j.neuro.2012.06.014.*

III. Juran S, van Thriel C, Kleinbeck S, Schäper M, Falkenstein M, Iregren A, Johanson G (submitted). **Electrophysiological correlates of impaired response inhibition during human inhalation exposure to propionic acid**.

IV. Juran S, van Thriel C, Kleinbeck S, Schäper M, Falkenstein M, Iregren A, Johanson G (Manuscript). **Is smelly different from toxic? An ERP study in human volunteers during inhalation exposure to cyclohexylamine and ethyl acetate**.

CONTENTS

LIST OF ABBREVIATIONS

LIST OF DEFINITIONS

Affect: The pre-personal emotional expression of feelings.

Amygdala: From the Greek word for almond, due to its shape. Group of nuclei within the temporal cortex of the brain with functional involvement in emotions and memory.

Association fibers: Bundles of axons inside the brain with the function to connect different parts of the brain.

Attention: A cognitive function to select parts of the environment for processing and ignore others. For example, I attend my PC monitor and ignore the sounds around me.

Cognition: A group of mental functions for information processing like attention, memory, and problem solving. “Cold” cognition has long been contrasted with “hot” emotions.

Cortex: Latin for bark. Cerebral cortex is the outer layer of the brain that is subdivided in four clearly separable parts: frontal, parietal, temporal, and occipital cortex.

Crossmodal integration: Perceptions from more than one modality (vision, audition) are processed together in the brain. This can cause mutual enhancement or interference.

EEG: Electroencephalography is a non-invasive method to record neural activity from the scalp with very good time resolution (milliseconds.

Emotions: Feelings that are expressed in a social context for the purpose of social interaction. They are tightly linked to evolutionary evolved goals of survival relevance. Emotions are displayed in a two-dimensional space of unspecific arousal (high, low arousal) and hedonic valence (pleasant, unpleasant).

Enantiomers are substances with identical molecular structure but mirrored geometrical positioning of functional groups.

ERP: The event related potential is a special EEG technique with which the EEG waveform can be interpreted in relation to cognitive processes.

Feelings: Are affects that can be classified and described, based on personal experience.

Glomerulus: Spherical structure where olfactory receptor neurons from the nose enter the first olfactory relay station, the olfactory bulb.

Heteromodal cortex: Cortical brain region that processes information from many modalities. See also unimodal cortex.

Hippocampus: Brain structure in the depth of the temporal cortex with functional involvement in memory processing and orienting in space.

Hypothalamus: Group of small nuclei in the depth of the brain, involved in linking the central nervous with the endocrine system.

Inhibitory interneurons: Neurons that connect nearby regions within one brain area to reduce their activity.

Instrumental reinforcers: Expression from learning theories where the positive outcome of a behavior in form of reward (reinforcer) modifies behavior.

Locus coeruleus: A nucleus that is part of the brain stem. It sends noradrenaline projections to the whole brain and promotes homeostasis in and between many systems (arousal, attention, emotion, balance, stress).

Multimodal: Processing information from more than one modality.

Multiple chemical sensitivity: Chronic medical condition in which low-level chemical exposure evokes vague symptoms of for example irritation nausea, or fatigue.

N2, nogo-N2: Components of the event related potential (ERP) with special characteristics explained in *chapter 5*.

Odorant: A volatile substance that is potent to activate olfactory receptors and to evoke an odor percept.

Odor molecule or molecular feature: The simplest units (atom groups) of an odorant. They seem to determine binding at the olfactory receptor level.

Olfactory bulb: First relay station for processing of olfactory stimulation in the brain.

P3, nogo-P3: Components of the event related potential (ERP) with special characteristics explained in *chapter 5.1.*

Perception: Organization, identification and interpretation of sensory information in order to represent and understand the environment.

Pyramidal neuron: Among the largest excitatory neurons of the brain occurring in cortex, amygdala and hippocampus.

Synaptic plasticity: The connection (synapse) between two neurons can change in strength, related to former (co-) activation.

Thalamus: Brain relay station that connects sensory and motor signals and regulates consciousness and alertness.

Trigeminal nerve: Largest of the cranial nerves (CN 5) reaching the whole face. It mediates for example chemosensory pain perceptions like stinging.

Unimodal cortex: Cortex brain region that processes information from only one modality, like vision.

Valence or hedonic tone: are stimulus characteristics which are potent to evoke affect, feeling or emotions.

Volatile: Substances that are readily vaporized with boiling point at a relatively low temperature.

1 BAD SMELLS – WHY BOTHER?

We do bother about the air we smell! Public complaints of perceived air pollution with significant contribution of olfactory nuisance have remained high during the past 30 years despite remarkable improvements in air quality (Donham, 2010). At the same time indoor air has gained importance since we spend up to 90% of our lives indoors, which led the World Health Organization (WHO) to the following statement: *"Healthy indoor air is recognized as a basic right"* (p. XI, *Guidelines for indoor air quality*, WHO 2009). However, warranting this basic right to everyone has proven difficult and individual health syndromes of chemosensory intolerance like 'Sick Building Syndrome' or 'Multiple Chemical Sensitivity' have been identified (Hodgson, 2002; Norbäck, 2009), which indicate the health relevance of air quality. Finally, in the working environment chemosensory effects are a major issue as recently reviewed by (P. H. Dalton & Jaen, 2010). For example have 20% of Swedish employees reported their discontent with indoor air quality at work (Norbäck, 2009). At industrial workplaces the problems are probably worse, since in the USA and Sweden about 40% of occupational exposure limit values (OEL) concern local irritants. Local irritants are substances whose critical health effect is irritation of the upper airways and the eyes (Dick & Ahlers, 1998; Edling & Lundberg, 2000). OELs for local irritants are set to avoid pain-like perceptions like stinging or burning which are mediated by the trigeminal system; however, it can be assumed that most of such irritant substances evoke olfactory perceptions already at lower levels (D Shusterman, 2001). Thus, at least 40% of OEL regulated substances ban be expected to evoke chemosensory perceptions at regular workplace conditions and it can be assumed that such continuous exposure has an impact on cognitive functioning comparable to noise (Persson Waye, Bengtsson, Kjellberg, & Benton, 2001). Although there is no comprehensive theoretical concept, the olfactory system is widely assumed to comprise evolutionary functionality as a warning modality, for example when we detect fire or spoiled food. I will describe this topic in more detail in chapter *2.1 Olfaction, evolution and emotions* (Stevenson, 2010). This assumption has led to the postulation that presence of chemosensory stimulation might activate an automatic call

for attention, thereby causing interruption of concurrent cognitive processes. It was the main question of the current thesis to examine if this postulation is true.

One example for an earlier investigation of this question is the study by Wyon, showing that task performance in an office environment improved with improved air quality for example by enhanced ventilation or removal of odor sources (Wyon, 2004). Regarding industrial workplaces chemosensory exposure and its potential cognitive interference has also been repeatedly discussed as a possible cause of risk (Dick & Ahlers, 1998; Rohlman, Lucchini, Anger, Bellinger, & van Thriel, 2008). However, experimental examination of this topic has been scarce and cannot yet provide convincing support for the proposed chemosensory distraction.

Van Thriel and colleagues in Dortmund have published neurobehavioral results from human inhalation exposure studies using four different volatile compounds in an extensive study design enabling within-subject comparison from performance during varying exposure concentrations (Kleinbeck et al., 2008; C van Thriel, Kiesswetter, Blaszkewicz, Golka, & Seeber, 2003; C van Thriel et al., 2007). Despite clearly elevated subjective ratings of (annoying) chemosensory exposure, no unequivocal indication for a distraction effect was found for the tested cognitive functions (divided attention, sustained attention, working memory) and the examined substances (ethyl acetate, 1-octanol, isopropanol, and 2-ethylhexanol) at exposure concentrations corresponding to current OEL values. Instead, results indicated that a subpopulation of healthy people who considered themselves as being especially sensitive to chemosensory stimuli seemed to be more susceptible for the distracting effect of chemosensory stimulation (C van Thriel, et al., 2003; C van Thriel, et al., 2007).

Based on these findings it was examined if chemosensory stimulation interferes with cognitive processes. The following points were regarded of special importance and will therefore be introduced in detail in the following: *First*, olfaction varies in many aspects from other senses like vision. Characteristics are found on level of the olfactory neural network, they exist in form of its functional implication as a warning modality and they occur as the special emotional effect odors have. *Second*, emotions on the other hand

acquire enhanced perceptual processing and have been shown to be especially potent to interfere with other ongoing cognitive processes. *Third,* cognitive inhibition processes have been shown closely related to emotional evaluation. These points together build the basis for task selection in the empirical studies that build the current thesis.

2 OLFACTION

2.1 OLFACTION, EVOLUTION AND EMOTIONS

In the beginning I want to stress some unique aspects of olfaction, which I think are of relevance for the current thesis. The first aspect is the recurring discussion of special evolutionary relevance in olfaction, which is stressed since literally all living organisms, from bacteria to elephants and human beings possess some sort of chemosensory perception system. For some life forms chemosensation is of such high relevance that it exclusively determines locomotion (chemotaxis). In human beings olfaction also touches many areas with survival relevance. Ingestion is guided by olfaction at the steps of food detection, evaluation and selection. Furthermore, olfaction is of high relevance for satiety processes and together with learning and reward mechanisms it promotes diversity by which it contributes to balanced nutrient uptake. Another area with major contribution of the olfactory senses is hazard avoidance, which includes the classical example of fire-smoke detection but also touches disease avoidance by evoking disgust. Finally, the role of chemosensory signaling in social communication like mating choice or avoidance of inbreeding is currently a hot research topic (Lundström, Olsson, & Gerald, 2010). All points have been exhaustively reviewed for humans by Richard Stevenson (Stevenson, 2010).

The role of olfaction as described above shows some striking similarity to what will be defined as *Emotions* in a *chapter 4*. Imagine the pleasure of smelling a freshly baked pizza when rushing home hungrily, the disgust when realizing that the sandwich you've eaten was made of moldy bread, the objection towards a dish you recently had a bit too much of, the sickness that immediately gets hold of you when smelling vomit, the fear and arousal when you suddenly smell fire smoke, and finally the passion you feel when smelling the shirt of your beloved one. All these examples illustrate the strong emotional dimension of odors and olfaction.

Another fact that odor perception and emotions have in common is a close relationship with autonomous responses like changes in heart rate and respiration, a dry feeling in

the mouth and sweaty hands. Such physiological activation via the autonomic nervous system (ANS) has been discussed as a characteristic of emotions already on century ago (James, 1884; Lange, 1912). The purpose of such physiological activation is assumed in activation of the organism in a fight-or-flight response. Processing of hedonic stimuli is fast and in some situations pre-attentive, in consequence they are assumed to exert an alerting function. The same could be true for olfactory stimuli. Thus odor intensity has been shown to modulate skin conductance whereas odor valence evoked heart rate changes (Bensafi, Rouby, et al., 2002a, 2002b). Other studies have even shown odorant specific patterns of ANS activation, indicating the relevance of olfactory stimuli for activation of a specific ANS response (Alaoui-Ismaili, Robin, Rada, Dittmar, & Vernet-Maury, 1997). Early amygdala involvement in neural olfactory processing is a likely source for this early ANS activation.

The close relation between olfaction and emotion might have its roots in the molecular structure of odorants. Thus, a recently developed mathematical model based on physicochemical odorant properties was able to predict hedonic valence (Khan et al., 2007). Furthermore, perceptual odor space, as represented by ratings of odorant descriptors, was best represented by odor valence. These results indicate that pleasantness is the main characteristic that our olfactory system extracts from decoding physicochemical properties of an odorant. A recent article even argued that hedonic valence is the only perceptual dimension of odors (Yeshurun & Sobel, 2010). An immanent coding of hedonic tone based already in the molecular structure of odorants further stresses the importance, and possibly the effectiveness, of the pleasantness or unpleasantness of odors.

This aspect of emotional potency of the olfactory system is regarded of high relevance for the chemosensory distraction hypothesis since it has been shown that emotional stimuli and especially unpleasant emotional stimuli may have a special potency to distract from ongoing cognitive processes. This will be described in chapter *4 Emotions.*

2.2 NEUROANATOMY OF OLFACTION

In the following I will take a closer look at neural networks underlying olfactory processing. This is a very restricted view, since the olfactory system has exceptionally strong links to the trigeminal and the taste system. Together they constitute the chemosensory system. I will use the term chemosensory occasionally when the context does not allow assuming exclusive olfactory mediated processes. For more information on the chemosensory system I refer to two recent reviews (Lundstrom, Boesveldt, & Albrecht, 2011; E. T. Rolls, 2005).

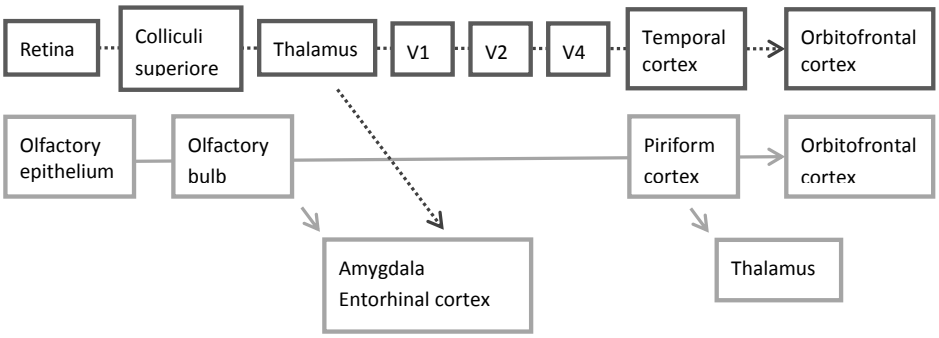

Figure 1: Schematic neural pathway for visual (top) and olfactory (bottom) modality showing only the most important projections. The focus lies on the shortness and early branching of olfactory but not the visual system. For exhaustive picture of olfactory neural processing, see for example (Doty, 2003).

Olfaction differs from other senses in many aspects. It is the only sensory system whose receptor neurons have direct contact with the environment via olfactory receptors in the nasal mucosa. Probably due to this exposedness, olfactory receptor neurons are constantly renewed during lifetime. The neural pathway for processing of olfactory stimuli is rather short and broadly branched at a very early level of processing, which is indicated schematically in *figure 1*. Early projections to heteromodal brain regions involved in emotion processing (amygdala) and memory building (entorhinal cortex) are indicated.

Furthermore, in contrast to other senses (e.g. visual system) we know comparably little about olfactory neural pathways. This is in part due to the fact that it was only about two decades age that Buck and Axel discovered the gene family expressing olfactory

receptors which formed the basis for understanding of olfactory perception at the receptor level (Buck & Axel, 1991). Since then, substantial progress has been made but there are still many basic questions open today. Although we now know of about 350 different olfactory receptors in the human olfactory epithelium (compared to four receptor types in human retina) there is no way to predict binding (or not) of a given volatile molecule, or to predict the perception that will (or will not) evoke after olfactory receptor activation. Indeed it has been shown that molecule enantiomers can be perceived differently by human volunteers (Laska, 2004), indicating that not only the molecular structure of a volatile compound but also the geometric position of its functional group determines receptor binding and thereby the odor percept. Furthermore, the organization of olfactory input is not fully understood. A recent study indicated that coding at the receptor level is organized along a pleasantness access (Lapid et al., 2011), whereas organization on olfactory bulb level seems to represent molecular characteristics (see *chapter 2.4*). Coding on primary olfactory cortex is still unclear but it is assumed that it promotes recognizing and differentiation of odor objects (see *chapter 2.5*). Finally, higher levels of olfactory processing are also poorly understood, like the tendency in humans to process and perceive odors without consciously attending them or our relative inability to recognize and identify even very common, everyday odors (Richardson & Zucco, 1989; Wilson & Stevenson, 2006).

I will now give an overview of neural projections and their functional implications in the olfactory pathway, as they are known today. The main sources for this chapter are a range of recent review articles (I. Savic, 2001; Shepherd, 2005; Wilson & Sullivan, 2011) as well as standard books of olfactory research from Wilson and Stevenson (Wilson & Stevenson, 2006) and Richard Doty (Doty, 2003). Regarding terminology, I use odor(ant) or odor molecule when referring to a volatile substance that is potent to activate olfactory receptors and evoke an odor percept or smell. Molecular features and odorant functional group are used interchangeable meaning groups of atoms in odor molecules. It is assumed that the reader is familiar with basic concepts of neural and perceptual processing in the human brain from the level of receptor activation to primary sensory cortex, higher unimodal association cortex and finally heteromodal cortical integration.

A good overview is given for example in an early review on visual processing (Mesulam, 1998).

2.3 OLFACTION ON THE RECEPTOR LEVEL

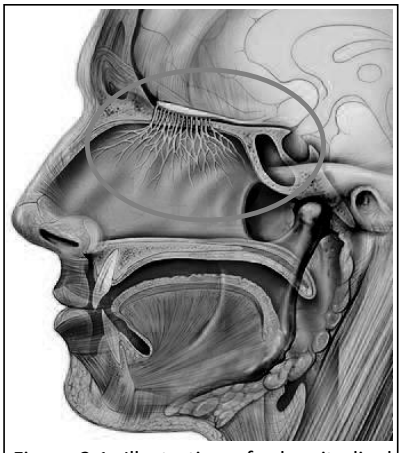

Figure 2.1: Illustration of a longitudinal section through a human head showing nasal cavity with olfactory receptor nerves expanding from olfactory bulb (circle). Illustrator Patrick Lynch http://patricklynch.net.

First level of contact for an odorant molecule is the olfactory receptor, located in a protective mucus layer on the olfactory epithelium at the upper end of the nasal cavity. See *figure 2.1*. Olfactory receptors are expressed on olfactory receptor neurons with only one receptor type occurring on each neuron (one receptor-one neuron rule). Olfactory receptors are not substance specific, but instead respond to specific functional groups of the odor molecule like carbon chain length. In addition, olfactory receptors vary in their tuning (some respond to many, others to few functional groups) and show overlapping specificities (many receptors respond to the same functional group). This complicated pattern of receptor responsiveness evokes a complex and odorant specific binding pattern at the olfactory receptor sheet. Such receptor coding promotes the processing of even unfamiliar substances due to the high probability that at least some molecular features can be bound at the olfactory receptor, but it has the disadvantage that odorants of a mixture will be hard to separate, since there is no way to separate mixture components. Neural projections reach the olfactory bulb as next level of processing.

2.4 OLFACTION IN THE OLFACTORY BULB

Olfactory receptor neurons project ipsilateral[1] from the receptor sheet to the first olfactory relay station, the olfactory bulb. Each olfactory receptor neuron that expresses the same receptor type projects to the same olfactory bulb region, leading to convergence of related signals and thereby their enhancement. Olfactory bulb glomeruli are spherical structures where axons of the receptor neuron meet the olfactory bulb's main in and output fibers (mitral and tufted cells). Each glomerulus expresses a receptor specific activation pattern for a given odorant and adjacent glomeruli receive projections from olfactory neurons with similar receptive fields. Spatial coding in olfactory bulb therefore seems to be organized by molecular features, as compared to visual retinotopic coding in the primary visual cortex and to auditory tonotopic coding in the primary auditory cortex. Activation of olfactory bulb is further regulated by inhibitory interneurons supporting for example temporal integration or contrast enhancement between adjacent glomeruli. The goal of this interneuron network is to facilitate binding of simultaneous molecular features, which is of essential importance for generating a perceptual odor object. One drawback at this level of processing is the lack of object-ground separation; that means that the smell of for example coffee is combined with all background odors and evokes one global pattern of olfactory bulb activation, making it impossible to discriminate two odor sources.

A special characteristic of the olfactory system is the heavy branching already on this early level of processing. For the current work I will focus on a selective description of brain areas that are involved in human olfaction and for which hypotheses about their functional relevance exist. Since I assume that the emotional potency of odorants might contribute to the proposed chemosensory distraction effect, I will describe olfactory pathways involving brain areas of emotional processing like the amygdala and the orbitofrontal cortex (OFC). For exhaustive overview on olfactory system connectivity in mammals, see for example (Cleland & Linster, 2003).

[1] Ipsilateral: Neural projections reaching only one half of the brain (left/right hemisphere).

2.5 OLFACTION AND THE PIRIFORM[2] CORTEX

Mitral and tufted cells of the olfactory bulb represent second order neurons that project to a range of different cortical structures of which the piriform cortex is the main target. Olfactory bulb output to piriform cortex is both diverging (one glomerulus to many piriform neurons) and converging (different glomeruli to the same piriform neuron) and terminates on pyramidal neurons in the piriform cortex. These pyramidal neurons are connected by intra-cortical association fibers, which show synaptic plasticity in order to link and remember distant co-activation. The purpose of this association network is first, to synchronize simultaneous activation, and second, to remember and enhance it when it occurs the next time. Such combination of *current* olfactory bulb input (receiving activation pattern of what I smell now) together with memory of *past* activation pattern (refreshing connectivities that co-occurred earlier via association fibers) is called autoassociation and helps the system to recognize familiar odor objects for example in form of pattern completion. That means, when an incomplete but familiar odorant reaches the olfactory receptor level, it evokes a fragmentary representation at the level of the olfactory bulb. However, the association network at piriform cortex level is able to remember the combination and enhance it so that even the missing parts will be co-activated, which supports recognition. This mechanism helps to stabilize and discriminate all odor objects, giving piriform cortex the capacity to synthesize, store and recall incoming olfactory bulb pattern. For further description and interpretation of olfactory processing on the level of piriform cortex, see (Wilson & Sullivan, 2011).

Main target region of piriform cortex output is the orbitofrontal association cortex. Further connections comprise the anterior nuclei of the thalamus, hypothalamus, amygdala, the hippocampus as well as the insular cortex (Cleland & Linster, 2003). Based on these wide range of early interconnections with brain areas involved in memory (hippocampus) and emotional processing (amygdala) as well as with heteromodal cortices, Donald Wilson and Richard Stevenson have recently developed a learning based theory of olfaction that assumes that odor percepts are generated at piriform

[2] Piriform: having the form of a pear.

cortex level where they are already tightly linked to information provided by other modality (Stevenson & Boakes, 2003; Wilson & Sullivan, 2011). The authors assume this feature to be the basis for many multimodal odorant descriptions like the sweet smell of vanilla. This approach will be addressed in the summary *chapter 2.8* as well as in chapter *9 Results and discussion*.

2.6 OLFACTION IN HETEROMODAL ORBITOFRONTAL CORTEX

In the next step, olfactory projections reach heteromodal association areas like the medial and lateral orbitofrontal cortex (OFC). The contribution of these heteromodal brain areas to olfactory perception is still not clear (Shepherd, 2007). One difference to other modalities is that OFC in olfaction serves as both unimodal and multimodal association cortex, which again gives support for the above named potential multimodal connectivity.

Human OFC in general has been assumed to participate in coding of hedonic stimulus valence, which was for example shown by Royet and colleagues who reported OFC activation following hedonic but not neutral stimuli in the visual, auditory and olfactory modality (Royet et al., 2000). Later studies indicated also gradual coding of hedonic stimulus dimension in OFC since its activation was correlated to odorant pleasantness ratings, whereas piriform cortex correlated to odorant intensity (Grabenhorst, Rolls, Margot, da Silva, & Velazco, 2007). In addition, OFC activation is influenced by semantic information, which has been shown in an elegant study by de Araujo and colleagues (de Araujo, Rolls, Velazco, Margot, & Cayeux, 2005). In a brain imaging paradigm, the authors provided one odorant, isovaleric acid, in two conditions once following the verbal descriptor 'body odor' and once following 'cheddar cheese'. Results showed that medial OFC activation was enhanced when 'cheddar cheese' was given as a semantic descriptor and this modulation was again correlated to pleasantness ratings. These results indicate strongly that the medial OFC[3] is a region of integration for conscious,

[3] Note that this medial OFC region is located close to anterior cingulate cortex, which is involved in response inhibition (see chapter *5 Cognitive control and inhibition*).

cognitive processes with olfactory pleasantness representations. This functional integration probably promotes conscious evaluation of emotional stimuli, an assumption supported by findings from Royet and colleagues who found that OFC was activated when active judgment of the odorants' hedonic valence was required as compared to passive smelling (Royet, Plailly, Delon-Martin, Kareken, & Segebarth, 2003).

From the data presented so far it can be concluded that OFC activation is part of conscious and controlled stimulus processing, that it contributes to evolvement of pleasantness and that it integrates semantic information (odor labels) with the generated stimulus evaluation. These findings fit with the assumed general role of heteromodal OFC in stimulus reward learning and stimulus evaluation (Royet, et al., 2000). A detailed description of this reward learning theory, comprising neural network organizations, animal models, and human imaging data, is given in (Edmund T. Rolls & Grabenhorst, 2008).

2.7 OLFACTION IN EMOTIONAL BRAIN AREAS: THE AMYGDALA

The amygdala is an almond shaped region in the middle of the temporal lobes. Its involvement in unpleasant odors has already been indicated in early human imaging (Zald & Pardo, 1997). Later studies generalized this observation to the visual, but not the auditory, modality (Royet, et al., 2000), which led to the assumption of general amygdala involvement in hedonic stimulus processing. In olfaction this functional role seems to be different, since even relatively neutral olfactory stimuli activated amygdala in a passive smelling paradigm, when contrasted with passive perception of odorless air. Other structures that were co-activated in this condition were piriform, insular and orbitofrontal cortex (Ivanka Savic, Gulyas, Larsson, & Roland, 2000). Support for such a special, non-emotional role in olfactory stimulus processing was also found in intra-cerebral EEG recording in epileptic patients (Hudry, Ryvlin, Royet, & Mauguiere, 2001). The study showed amygdala activation evoked by a variety of everyday odorants including the neutral odorant butanol but not by odorless air. Latencies of this amygdala activation indicated that they stem from back-projections to the amygdala region from a

later state of olfactory processing (following odor detection). In conclusion, it seems given that amygdala is strongly involved in processing of olfactory stimuli but the nature of its contribution in humans has to be examined in more detail (e.g. discussed in J. A. Gottfried, Deichmann, Winston, & Dolan, 2002).

One interesting amygdala aspect that has been examined in an animal model is its central role in fear conditioning, where a fast and enduring association is formed between neutral stimuli (sound) and intrinsic fear stimuli (electric shock). Amygdala activation has been shown to provide the link between stimulus representation (sound) and emotional response (fear). This aspect will be described in more detail in chapter *4.2 Neuroanatomy of emotions*. In olfaction, it has been shown that classical conditioning occurs especially fast and that it seems more resistant to extinction than in other modalities (Lawless & Engen, 1977). Early amygdala involvement in the olfactory processing stream could be one source contributing to this enhanced olfactory conditioning. Finally, odor pleasantness coding has been assumed to be related to odorant molecular structure (Khan, et al., 2007), as I indicated in chapter *2.1 Olfaction, evolution and emotions*. Early amygdala involvement to the olfactory processing stream might contribute to this phenomenon (see *figure 1*).

2.8 SUMMARY AND CONLUSION I: OLFACTION AND EMOTIONS

This short neuroanatomical overview of olfactory processing shows a characteristic feature of the olfactory system. Olfactory stimuli have a short path of neural processing, reaching heteromodal brain areas like amygdala and orbitofrontal cortex already at the third neural synapse from the receptor level (see *figure 1*), which means that no unimodal higher association cortex exists. This is true for both brain areas discussed above, OFC and amygdala, which are known for involvement in emotional processes. An interesting functional implication resulting from this is that olfactory stimuli are more tightly linked to sensory input in other modalities. I refer to the *Mnemonic theory of odor perception*, which proposes that the odor percept itself is multimodal, not only representing chemosensory specific object features but also for example visual or taste aspects. This functionality is assumed to support odor object recognition and object-

ground separation, two processes that are yet not fully understood in olfaction. Congruent visual stimulation has been shown to facilitate odorant detection, supporting this assumption (Jay A. Gottfried & Dolan, 2003).

Furthermore, exceptional emotional properties have been proposed for olfaction on the level of electrophysiological responsiveness (early ANS modulation), on the level of brain activation (amygdala involvement), and due to the evolutionary relevance of olfaction with close relations to immanent survival goals of highest priority (see *chapter 3 Emotions*).

Both points, close connectivity to representations of other sensory stimuli and emotional and evolutionary relevance, support the possibility that odorants interfere especially easy with processing in other modalities. This conclusion supports the main assumption of the current thesis, that olfaction can influence concurrent processes in other modalities. This emotional aspect served to derive *valence hypothesis II*, which is presented in *chapter 7*.

3 OLFACTION AND COGNITION

Another prominent characteristic of olfaction is the special form of thalamus involvement. The thalamus is a midbrain structure that is traditionally assumed to mediate attended or aware stimulus representation and in other modalities it is usually approached on a relatively early level of neural projections that is prior reaching primary sensory cortex. For olfaction, thalamic connectivity has long been a topic of debate leading to the assumption that odors cannot be addressed willingly at all. For detailed description of attention processes see chapter *5 cognitive control*. But even after identification of thalamus projections, the exceptional position of olfaction remained, since thalamus integration to the neural olfactory pathway occurred at a unique processing step, following primary olfactory cortex (piriform cortex) involvement, which is indicated in *figure 1*. Since the main topic of this thesis is the interaction between olfaction and cognitive processing, a short overview is given in the following. First point will be to address effects of cognitive modulation within the olfactory modality, and then I will address the point of influences between modalities, of which visuo-olfactory interactions have been examined the most. Finally I will give a short overview over earlier studies addressing the question of olfactory mediated cognitive impairment.

The relationship between olfaction and cognition has started to be investigated in the beginning of this century. Charles Spence and colleagues showed that directing attention to olfaction, instead of vision, enhanced olfactory target detection, which was a clear demonstration of attended processing of olfactory stimuli (Spence, Kettenmann, & McGlone, 2001). Later on, human brain imaging studies have shown olfactory attention effects in the primary olfactory cortex (piriform cortex[4], see (Zelano & Sobel, 2005). This result is comparable to the visual modality where visual attention enhances primary cortex activation. Interestingly, emotional content seems to have the same effect, which is enhancement of primary visual cortex activity (Vuilleumier & Driver, 2007). Nevertheless, olfactory attention effects on piriform cortex seem to differ from other

[4] Olfactory processing at piriform cortex level is described in chapter *2.5 Olfaction and the piriform cortex.*

senses, since piriform cortex activation has been shown to vary between cognitive task aspects like odor recognition or odorant memorization. Such variability has not been shown for example in the visual modality (discussed in (Zald & Pardo, 2000). However, cortical adaptation or habituation mechanisms that have been shown to evolve on piriform cortex level may contribute to such task inconsistencies. For an exhaustive review on attention and olfaction, see (Keller, 2011)

3.1 OLFACTION AND OTHER PERCEPTIONS

Up till now I presented a selection of basic knowledge about olfaction and cognitive control systems. Another important question to approach when examining chemosensory distraction is the potential of odors to interact with perceptive and cognitive processing in other modalities. I will focus on interactions with the visual modality, since this is the best examined modality and since these were the modalities examined in the current thesis.

In general, many levels of interaction are possible when two stimuli are given at the same time. They can enhance or interfere with each other on the perceptual level, the level of cognitive processing, the level of response selection, or the level of motor activation. Furthermore, different experimental paradigms can challenge different cognitive functions that are influenced individually by co-occurring stimuli. Finally, focus in multimodal processing can be set on supportive mechanisms (stimulus binding) or on interfering, as the proposed chemosensory distraction hypothesis. An overview over the field in general is given in (Calvert & Thesen, 2004) and some implications from the chemosensory senses are given in (Small, 2004). In the following I will describe a selection of studies that have shown different kinds of interaction between the olfactory and visual modality.

Already in the introductory section of this chapter, I mentioned the question which role cognitive control processes like attention have on the olfactory modality. I referred to evidence from the behavioral level and from brain imaging studies, showing that attention effects have been found in olfactory processing which are comparable to the

visual senses. Spence and colleagues furthermore concluded that a common cognitive control mechanism serves processing in both modalities since invalid cues, that directed attention to non-target modality (e.g. visual), impaired processing in the other (i.e. olfactory) modality (Spence, et al., 2001). This is an important finding for the current thesis since existence of a cross-modal chemosensory distraction effect assumes the existence of one supramodal cognitive control system instead of many parallel and modality specific control systems that do not interact with each other. See (Spence, et al., 2001) for detailed discussion of this topic in the visual and chemosensory senses. In general support for supramodal organization of cognitive control has been gathered during the last decade (Calvert, 2001).

Nowadays the prevailing opinion even assumes that olfactory processing is especially easy to influence from other sources of information. In an early series of studies, Pamela Dalton showed that information given about a perceived odorant was a stronger source for evaluation of the chemosensory perception or its evoked symptoms than the odorant itself (P. Dalton, 1996, 1999; P. Dalton, Wysocki, Brody, & Lawley, 1997). Following the same line of argument, recent brain imaging studies showed that semantically congruent stimulation in the visual modality (both pictures and names) was able to both speed up olfactory detection (Jay A. Gottfried & Dolan, 2003) as well as modulate pleasantness ratings (de Araujo, et al., 2005; Djordjevic et al., 2008). More detailed discussion of these studies has been given in chapter *2.6 Olfaction in heteromodal orbitofrontal areas*.

Another aspect of high relevance for the current thesis is the effect chemosensory stimulation has on visual processing. Facilitating effects of olfactory stimulation on a visual exploration task including complex stimuli has recently been shown on the behavioral level (Seigneuric, Durand, Jiang, Baudouin, & Schaal, 2010). Especially interesting in this study was that the reported effects depended on semantic congruency between the olfactory (orange smell) and visual (orange picture) stimuli but not on conscious perception of the olfactory stimulus. This effect demonstrates a very interesting ability that odorants seem to have in common with emotional stimuli, which is that they influence behavior in a pre-conscious level of processing (Morris, Ohman, &

Dolan, 1998). More detailed consideration of emotional stimuli and their processing will be given in chapter *4 Emotions*. The level of interaction for such cross-modal semantic interaction has been examined in an early event related potential paradigm (ERP) showing that semantic, contextual integration, which is represented in a negative ERP potential occurring at 400 ms following stimulus presentation (N400), was challenged when visual cues (orange) and olfactory background cues (rose smell) were semantically mis-matching (Sarfarazi, Cave, Richardson, Behan, & Sedgwick, 1999). Another ERP study showed crossmodal effects of an unpleasant odorant on a late positive ERP potential recorded during concurrent face evaluation only in hedonically congruent conditions (Bensafi, Pierson, et al., 2002). The authors interpret this effect in a way that unpleasant odorants especially pre-activate alerting arousal systems that promote reactions to potentially dangerous (unpleasant faces) stimuli. Together, these results let assume that information from all modalities is integrated to create a mental representation of the environment around us, and that this context in turn has the capacity to influence stimulus processing.

3.2 CHEMOSENSORY DISTRACTION – EARLIER STUDIES

I have shown so far en extensive picture of neuroanatomical basis of olfaction as well as strong evidence for prevalence of crossmodal effects between processing in the olfactory and visual modality. These premises have motivated researchers to examine chemosensory interference effects on cognitive processing.

However, evidence has so far been contradictory and I will describe some exemplary studies in the following. Hermans and colleagues (Hermans, Baeyens, & Eelen, 1998) showed that congruent olfactory primes improved subsequent emotional categorization of visual stimuli and that negative hedonic valence in general (prime and target) slowed down reaction times. On the other hand, (Millot, Brand, & Morand, 2002) and colleagues showed that exposure to both pleasant (lavender) and unpleasant (pyridine) background odors speeded up reaction times in visual and auditory choice reaction time tasks. The authors explain these effects by two different mechanisms, relaxation in case of positive

lavender as compared to increased arousal in case of unpleasant pyridine exposure. In a third example, (Michael, Jacquot, Millot, & Brand, 2003) and colleagues found that two pleasant ambient odors (mustard oil and phenyl ethyl alcohol) had contradictory effects. While mustard oil increased distractive effects in an attention capture paradigm (slower reaction times), phenyl ethyl alcohol reduced reaction times in the simple response paradigm but caused improvement during attention capture. The authors of this third study assumed that the trigeminal potency of mustard oil amplified the visual distraction effect of the attentional capture task, whereas the non-irritative phenyl ethyl alcohol somehow dampened stimulus processing. A suggested pathway is mentioned via the amygdala, due to its functional implications as early multimodal neuroanatomical relay station as described in *chapter 2*.

What is the reason for this inhomogeneity in olfactory distraction? One assumption is that different cognitive processes were challenged in different tasks and that not all are sensitive for chemosensory distraction. To be able to predict more reliably the sensitivity of cognitive function for olfactory mediated interference, I examine neuroanatomical models that explain mechanisms of cognitive control, emotional distraction and olfactory processing. Brain areas involved in all three mechanisms are assumed especially vulnerable for chemosensory distraction. In turn, cognitive processes that are known to be related to such brain areas are predicted to show olfactory interference effects

4 EMOTIONS

In this chapter I review some aspects of our basic knowledge about emotions and their underlying processes. A simplistic definition from which beneficial experimental approaches could be derived relates to the striving to achieve evolutionary evolved goals of survival relevance: "*… emotions are states elicited by instrumental reinforcers*." (Edmund T. Rolls & Grabenhorst, 2008), p. 231, line 3). Terminology related to emotion research is often confusing. *Affect* can be seen as a pre-personal emotional expression, like for example given by an infant. *Feelings* are instead affects that can be classified and described, based on personal experience. *Emotions* finally can be regarded as the expression of feelings in a social context and thus it comprises the purpose of social interaction. Instead *valence* or *hedonic tone* are characteristics of stimuli that are potent to evoke the above defined sensations. Emotional research mainly originates from observations of responding to hedonic stimuli or situations, hence the term used most often is emotion. Emotional measures are most often given in a two-dimensional space comprising unspecific arousal (high, low arousal) and hedonic valence (pleasant, unpleasant).

4.1 TIME COURSE OF EMOTIONS

Already earliest theories about emotions have included the phenomenon of immediate autonomic responses, measurable as for example heart rate or dermal conductance response. This feature is also present in olfaction, as stated in *chapter 2*. A nice review of the historical perspectives regarding the primacy of autonomous or central nervous responses in emotions is given in chapter three of "The Emotional Brain" (J. LeDoux, 2001).

This immediateness of emotional processing is a matter of research until today and automaticity of emotional stimulus processing is still examined in many experimental paradigms (for a review see (Compton, 2003). Support for superior processing of emotional stimuli has come for example from behavioral studies using fear-related

pictures (Ohman, Flykt, & Esteves, 2001) or emotional faces (Eastwood, Smilek, & Merikle, 2003) in visual search paradigms.

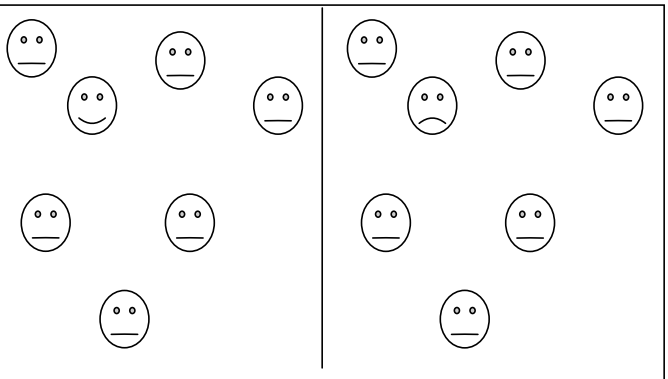

Figure 4.1: Example for an emotional visual search task, where sad target detection has been shown faster than happy target detection (Eastwood, Smilek, & Merikle, 2001).

The authors showed that increasing number of stimuli caused the expected increase in reaction times for target-detection of neutral or positive valence stimuli, but not for negative ones. Furthermore, hedonic stimulus valence enhances both perceptual (Phelps, Ling, & Carrasco, 2006) and cognitive processes (Adam K. Anderson, 2005; Eastwood, et al., 2001). Such findings gave support to the negative bias framework, assuming that negative emotional stimuli have an evolutionary relevance by which they gain preferential processing, irrespective of other concurrent perceptual demands. The cost for this unrestricted processing is a less detailed stimulus representation in bi-dimensional space (positive – negative) to support fast decisions making (approach, withdrawal) rather than detailed stimulus feature representations (Cacioppo, Gardner, & Berntson, 1999). How do our perceptual systems allow for such fast relevance evaluation in a flexible manner, without being caught up in hard-wired inescapable behavioral patterns that overtake for example the rat when smelling a cat?

In order to outline the time flow of emotional stimulus processing numerous ERP studies have been performed during the last decade and at least three reviews have been published recently (Hajcak, MacNamara, & Olvet, 2010; Olofsson, Nordin, Sequeira, & Polich, 2008; Schupp, Flaisch, Stockburger, & Junghofer, 2006). For an introduction to ERP technique, see *chapter 6*. Although putting different emphasis on different areas of the literature, the three papers agree in a two-step model of emotional stimulus

processing. In a first step, emotional stimuli draw attention in a rapid and unlimited way to enhance relevant stimulus processing, which seems to be mediated by arousal, instead of hedonic valence. Amplitude enhancements of an early positive peak (P160) and an early posterior negativation (EPN) have been shown following arousing stimuli and have been interpreted as boost in perceptual processing (Carretie, Hinojosa, Albert, & Mercado, 2006; N. K. Smith, Cacioppo, Larsen, & Chartrand, 2003) and stimulus discrimination respectively (Schupp, et al., 2006). In a second step of processing, emotional stimuli enhance a late positive potential (LPP) that seems to be closely related to the classic P3 components representing controlled cognitive functions of stimulus categorization and memory storage. It has been assumed that emotional and attentional modulation of stimulus processing draw upon the very same resources and could be influenced by the same neuromodulatory activity of the locus coeruleus norepinephrine system (Hajcak, et al., 2010). A functional modulation of P3 subcomponents by hedonic stimuli is indicated by Delplanque and colleagues, who showed in an oddball paradigm including distractor stimuli with varying valence that only P3b amplitudes were modulated by valence (negative > positive > neutral) whereas P3a amplitudes were related to distractor characteristics (Delplanque, Silvert, Hot, & Sequeira, 2005). This means that early orienting of attention, as indicated by P3a component of the ERP, is modulated by arousal, whereas higher cognitive processes like stimulus categorization and working memory integration, as represented by P3b, is sensitive for hedonic valence.

4.2 NEUROANATOMY OF EMOTIONS

In order to understand how some stimuli can be processed faster than others, I will describe parts of the rather detailed neuroanatomical model underlying emotional processing as it is known today. This knowledge is mainly based on pioneering work on classical conditioning of fear responses in the animal model (J. E. LeDoux, 2000) followed by human brain imaging studies (Luiz Pessoa & Adolphs, 2011) and research in patients with brain diseases (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004).

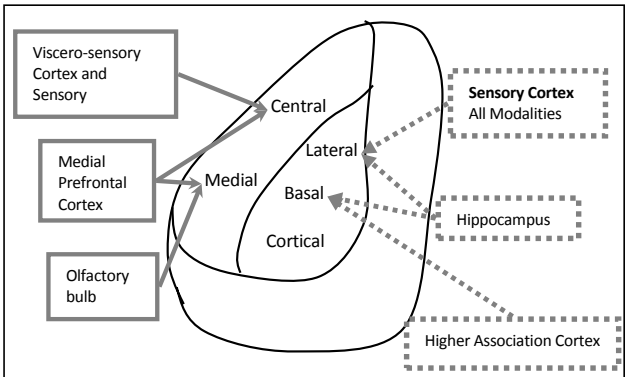

Figure 4.2: Schematic draft of the amygdala and its main nuclei displayed as evolutionarily primitive (left) and newer divisions (right, dashed). A selection of incoming projections is given. Figure modified after (J. LeDoux, 2007)

A key structure involved in emotions is the amygdala, which is located in the depth of the temporal cortex and which got his name from the Greek word for almond, due to its shape (see *chapter 2.7*). I already mentioned that one basic characteristic of emotions is the fast responding in the central and autonomic nervous system. In the animal model it has been shown that amygdala receives projections from all modalities (vision, audition) via the thalamus, the brain stem (pain) or the olfactory bulb (J. LeDoux, 2007). The interesting point about these early projections is that amygdala is informed about external occurring stimuli before this information can reach the primary sensory cortex, which is assumed to represent aware object representation. Amygdala outputs are widely distributed reaching hypothalamic and motoric regions in a reciprocal manner, allowing for fine-tuning feedback loops (J. LeDoux, 2001). To sum up, amygdala gets early thalamic sensory projections and has reciprocal connections to sensory cortices, which suggest that a first and probably imprecise thalamic projection has the function to pre-activate amygdala which on its part can modulate recurrent connections to cortical association areas for more fine-grained stimulus information.

Human brain imaging studies supported such amygdala involvement in enhanced processing of hedonic stimuli. Hedonic stimuli evoked stronger activation in amygdala, which correlated with enhanced activation of visual cortex and thereby explained improved performance as reviewed above (Lang et al., 1998; Morris et al., 1998). In addition, patients with amygdala lesions did not show this pattern of amplified visual cortex activation upon emotional faces (Vuilleumier, et al., 2004) and they did not gain from presentation of hedonic stimuli during the attentional blink paradigm (A. K.

Anderson & Phelps, 2001). The attentional blink describes the phenomenon that stimuli in rapid presentation series are suppressed when they precede a target in a given time span. This suppression is counteracted by hedonic stimulus content, but not in patients with amygdala lesions, indicating that amygdala is essentially involved in enhanced processing of hedonic stimuli. Neuropsychological models have been developed that integrate these findings to broader emotional networks (L. Pessoa & Adolphs, 2010; Tamietto & de Gelder, 2010).

5 COGNITIVE CONTROL AND INHIBITION

In the last chapter I reviewed evidence for the promptness and enhanced strength of hedonic stimulus processing and indicated a neural pathway via early amygdala projections for enhancement of primary sensory cortex activations. Such boost in processing initiated by stimulus characteristics (salience, contrast, color) is often described as 'bottom-up' mechanism. In the beginning of this chapter I now want to show another pathway that is potent to enhance stimulus perception via increased activation in primary sensory cortex regions, which are labeled 'top-down' mechanisms. Top down cognitive control describes selected enhancement of a subset of the complex environmental stimulation we are exposed to and this enhancement follows internal goals (e.g. cognitive task) instead of external ones (e.g. stimulus characteristics). As can be derived from name giving, bottom-up and top-down processes are related concepts and by close interaction they enable flexible adaptive behavior. Top-down cognitive control is an essential feature that enables us to act and pursue higher goals, instead of only reacting to the current context. A selected processing of a subset of all given stimulation is necessary since our perceptual and cognitive processing systems have restricted capacities. We simply cannot perceive and remember all things happening around us.

The earliest concept of a top-down selection mechanism is that of selective attention. One influential paradigm proving the existence of top-down selective attention was introduced by Michael Posner in the 1980s. He showed that covert attention that is directed to an optional point in space has the potency to enhance response speed in a subsequent target detection task, even without involvement of eye movements (Posner, 1980). He thereby proved that we can in a top-down manner optimize visual processing (enhanced response speed) by following an internal goal (focus on one location). The time course of this effect has been examined with ERP technology (for detailed description see *chapter 6*). In short, ERPs represent neural activation that promotes processing of a given event, in this case a stimulus. Comparing ERP following unattended and attended stimulus processing gives a clue about the time course of the underlying cognitive control effect. Such an exemplary comparison is given in *figure 5.1*.It can be

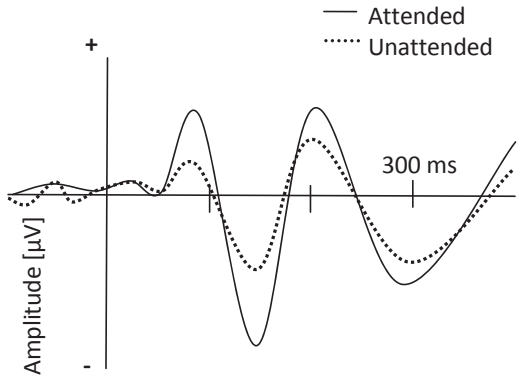

Figure 5.1: Event related potentials (ERP) following attended (——) and unattended (·····) presentation of visual stimuli.

seen that attention enhances curve peaks as early as 100 ms following stimulus presentation (named P1 or P100) and extend up till 300 ms. This indicates that top-down selection mechanisms effect perceptual processing on a very early step (100 ms) but that it also has an extending influence. For more detailed description see (Steven J. Luck, Woodman, & Vogel, 2000). An illustration of neuroanatomical networks supporting 'bottom-up' and 'top-down' mechanisms as described recently (Corbetta & Shulman, 2002) is given in *figure 5.2*. Classical higher order association cortices like prefrontal cortex and parietal cortex areas are involved. Note that both networks are localized close to each other, implicating their intimate collaboration in flexible behavior.

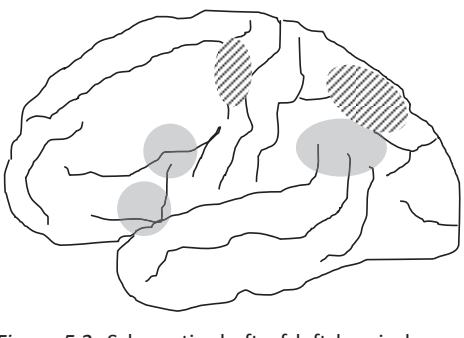

Figure 5.2: Schematic draft of left hemisphere of a human brain where neural networks are indicated representing 'buttom-up' (striped) and 'top-down' (gray) mechanisms for stimulus enhancement. Draft reproduced based on (Corbetta & Shulman, 2002).

Now I have described two stimulus selection mechanisms (bottom-up, top-down) and their assumed neural networks in parallel. However, it is obvious that both systems have to interact, like whenever accelerated and boosted hedonic stimuli occur without relevance for current goals like cognitive tasks. In such situations, inappropriate but immediate stimulus enhancement will pose a conflict to concurrent goals. To avoid interference with task performance, such conflict has to be detected and control mechanisms have to be initiated to solve the conflict.

Recently it has been a topic of high interest to investigate emotion inhibition processes and to examine in how far they differ from other processes of inhibition like cognitive, or response inhibition.

(Dillon & Pizzagalli, 2007) recently reviewed the neural basis for inhibition of cognitive, emotional or behavioral processes. The authors found indication for separable systems for each specific task together with common involvement of a general inhibition networks in frontal cortex. Response inhibition was related to a network connecting frontal cortex with basal ganglia, cognitive inhibition involved the orbitofrontal cortex, and emotion inhibition activated projections between ventromedial PFC and amygdala. Following this differentiation, I will describe findings regarding emotional and response inhibition separately.

5.1 RESPONSE INHIBITION (N2, NOGO-N2, P3, NOGO-P3)

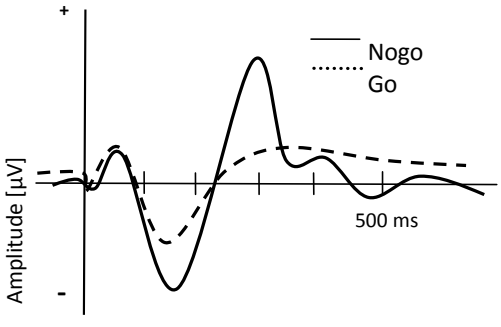

Figure 5.3: Event related potentials (ERP) following go (·····) and nogo (——) target presentation.

Response inhibition has been examined in a range of paradigms like the flanker task, the go/nogo task or the stop task (M. Falkenstein, 2006). Inhibition in the 'Stroop Task' however is more influenced by cognitive interference processes and will not be reviewed in the following. All paradigms of response inhibition have in common that they examine a situation where a given response tendency has to be suppressed, including situations where two contradictory response tendencies occur concurrently. Performance of response inhibition tasks have traditionally been examined on the behavioral level and with ERP. In general, tasks involving inhibition of a premature response tendency are slower and less accurate, which has led to subsequent examination of error performance (see chapter *5.3*

Cognitive control and error processing). ERPs following tasks involving inhibition usually show a fronto-central negative peak (N2, nogo-N2) at about 200 – 300 ms following target presentation, which is followed by a central positive peak (P3, nogo-P3) in the 300 – 400 ms time range (*figure 5.3*).

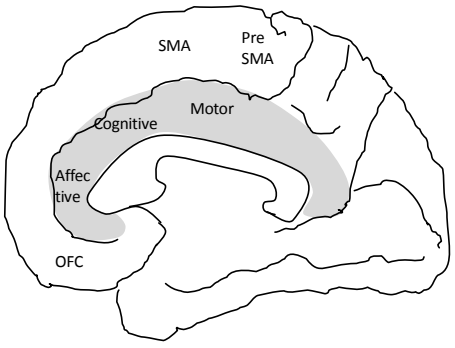

Figure 5.4: Schematic draft, right hemisphere of a human brain (medial). Networks involved in inhibition: anterior cingulated cortex (grey) with functional subdivisions, OFC orbitofrontal cortex, SMA supplementary motor area.

The functional relevance of these components is still under debate. One approach assumes that the N2 component represents activation of a general frontal alerting system to detect the need for cognitive control and that the subsequent P3 component represents behavioral adaptation mechanisms like response inhibition (Carter et al., 2000; Dimoska, Johnstone, & Barry, 2006). An extensive review on the N2 component in different experimental paradigms has been given recently by Folstein and colleagues (Folstein & Van Petten, 2008). Support for close relationship between nogo-P3 and response inhibition was for example provided by Janette Smith and colleagues (J. L. Smith, Johnstone, & Barry, 2007). In a cued go/nogo paradigm, the authors showed that predictive flanker evoked response preparation in form of a contingent negative variation (CNV) in the ERP. Amplitude of the target related nogo-P3 component varied with CNV thereby showing its connectivity to response mechanisms. In a follow-up study, the authors furthermore showed that this relationship was not dependent on mere motor execution since they recorded nogo-P3 also in a non-motoric target count task (J. L. Smith, Johnstone, & Barry, 2008). Generators underlying these inhibition related N2 components have been located in frontal brain regions which seem to be part of a general alerting system (Bokura, Yamaguchi, & Kobayashi, 2005). Bokura and colleagues recorded nogo-N2 and nogo-P3 peaks during a response inhibition task. Source localization indicated OFC and cingulate cortex as target regions for nogo-N2

generation and OFC as regions generating nogo-P3. These findings indicate the relevance of these frontal brain areas, ACC and OFC, in response inhibition tasks (*figure 5.4*).

5.2 INHIBITION OF EMOTIONS

Inhibition in the context of hedonic stimulation has been examined in many varying paradigms. Hedonic stimulus content can have task relevance or be an irrelevant context feature, which has been termed *direct* and *indirect affective task* respectively by some researchers (Albert, Lopez-Martin, Tapia, Montoya, & Carretie, 2012). In the following I will review evidence mainly from indirect affective tasks, since this experimental paradigm is comparable to the assumptions underlying the olfactory interference hypothesis. Albert and colleagues used positive, negative and neutral hedonic pictures to create an emotional background for performance of a go/nogo task (Albert, Lopez-Martin, & Carretie, 2010). On the behavioral level, reaction times were faster in positive as compared to both negative and neutral contexts, indicating facilitated responsiveness in positive situations. ERP analysis showed that this behavioral pattern corresponded to increased nogo-P3 amplitudes, a component that has been associated with response inhibition (see *chapter 5.1*). Inverse relatedness between nogo-P3 amplitude and reaction times supported this assumption. Source localization indicated anterior cingulate cortex as origin of the nogo-P3. These data were extended by the authors in a subsequent publication where they in addition showed that cingulate cortex varied with hedonic stimulus content (Albert, et al., 2012). These findings extend cingulate involvement from cognitive control mechanisms (see *chapter 5.1*) to emotional control mechanisms. Another study supported this finding on the electrophysiological level by showing that only nogo-P3 amplitude (but not nogo-N2) was increased by task irrelevant positive or negative emotional expressions on a facial gender discrimination task (Zhang & Lu, 2012).

A recent brain imaging study comparing emotional and cognitive conflict inhibition has shown a subdivision of cingulate cortex activity; activation in rostral cingulate cortex occurred only during emotional conflict, whereas dorsal cingulate cortex showed overall

involvement in conflict monitoring (Egner, Etkin, Gale, & Hirsch, 2008). Connectivity analysis in Egner's study indicated a relationship between rostral anterior cingulate activation and amygdala inhibition, supporting the assumption of an emotion regulation mechanism. Further evidence was provided by (Goldstein et al., 2007) and colleagues who showed increased dorsal anterior cingulate activation during response inhibition in negative as compared to neutral hedonic context. The same pattern of activation was found in medial orbitofrontal cortex, a brain region that has been interpreted as involved in emotional decision making (Edmund T. Rolls & Grabenhorst, 2008) as well as in accomplishing appropriate social behavior (Damasio, 1998).

Interestingly, one study using unpleasant olfactory stimuli to induce an emotional context in a mental fatigue paradigm showed comparable results of odor effects on nogo-P3 only (Kato, Endo, Kobayakawa, Kato, & Kitazaki, 2012). Instead of increased reaction times and reduced nogo-P3 amplitudes during performance of an extended go/nogo task in an odor control condition, both parameters remained unchanged when an unpleasant background odor was provided.

In conclusion, a network involving cingulate cortex and orbitofrontal regions seems involved in response inhibition tasks in the presence of hedonic stimulation. Cingulate cortex regions seem to be involved in emotional regulation as well as general alarming in case of interference (*figure 5.4*). Special effort seems to emerge when hedonic stimuli or a hedonic background are involved. The functional contribution of orbitofrontal cortex activation is not as clear, but involvement of emotional reward learning can be assumed. Kiss and colleagues showed in a facial go/nogo paradigm, that those faces serving as nogo targets were rated less trustworthy in subsequent ratings. These findings strongly suggest that response inhibition has a prominent role in stimulus evaluation (Kiss, Raymond, Westoby, Nobre, & Eimer, 2008).

5.3 COGNITIVE CONTROL AND ERROR PROCESSING (N_E, P_E)

The control of situations comprising conflicting information is prone to erroneous responses. Furthermore flexible and adaptive behavior is important in a changing

environment and a crucial feature is therefore that we are able to learn from erroneous performance. In consequence, the relationship between inhibition and error processing has been examined in a variety of tasks. In the following I will give a short overview over relevant findings from behavioral, electrophysiological and brain imaging studies.

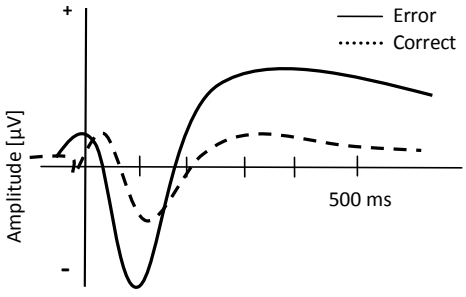

Figure 5.5: Response-locked event related potentials (ERP) following correct (.....) and erroneous (___) responses.

In the beginning of the 1990's two laboratories independently started to examine erroneous task performance using ERPs (M. Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Both labs described ERPs averaged to erroneous responses (and not to stimulus presentation) and found a pronounced fronto-central negative peak at about 100 ms (N_E, or ERN) that was followed by a central positive deflection at 300 ms (P_E), as given schematically in *figure 5.5*. Interpretation of these components has been under debate until today and four different theories exist trying to explain them: mismatch theory (Elton, Spaan, & Ridderinkhof, 2004), error detection theory (M. Falkenstein, 1997; Scheffers, 1996), reward learning theory (Holroyd & Coles, 2002), and conflict detection theory (Michael Falkenstein, 2004). Two recurring issues have been the question if the N_E can be differentiated from a group of N2 components that are evoked by mismatch detection (Coles, Scheffers, & Holroyd, 2001), or if it is not related to errors at all, since a comparable compound has been reported after correct responses in conflicting situations (Bartholow et al., 2005). Today, many studies have shown differential features of N2 and N_E components and have managed to localize their generating sources. Results indicate that the two components have both common generators in the medial prefrontal and anterior cingulate cortex area but also differing ones. Whereas error related activation seems mainly localized to anterior cingulate cortex, inhibition or conflict related activation seems to extend to mesial prefrontal cortex regions related to motor functioning like the pre-somatomotor area (Mathalon, Whitfield, & Ford, 2003;

Ullsperger & von Cramon, 2001). A comprehensive review on the topic has been given by van Veen and colleagues, who conclude that anterior cingulate cortex activation following target stimuli (N2) is involved in detection of conflict and in alerting of cognitive control mechanisms that are located in higher, frontal cortex areas (Vincent van Veen & Carter, 2002).

Anterior cingulate cortex activation following erroneous responses has a comparable alerting role that now calls for behavioral adaptation. Comparable interpretations can be found in (Garavan, Ross, Murphy, Roche, & Stein, 2002; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005). P_E component is assumed to serve this function by representing either behavioral adaptation (Vocat, Pourtois, & Vuilleumier, 2008) or the emotional component of an error (V. van Veen, 2002). Another brain area that seems to be relevant for error processing is the orbitofrontal cortex. Turken and colleagues showed that patients with orbitofrontal lesions were impaired in error correction which co-occurred with a reduced N_E amplitude (Turken & Swick, 2008).

Interestingly, error processing also seems to be influenced by emotions. This has been shown by two recent studies using hedonic picture material as background during (Larson, Perlstein, Stigge-Kaufman, Kelly, & Dotson, 2006) and immediately preceding (Wiswede, Münte, Goschke, & Rüsseler, 2009) performance of a flanker task. Both studies report differing results; Larson showed N_E amplitude decrease in unpleasant context whereas Wiswede showed N_E increase following unpleasant pictures. This difference could be explained by a distracting effect mediated by simultaneous presentation of flanker task and stimulus material during Larson's study, which might have drawn cognitive resources from the flanker task to picture viewing, leading to reduced error detection capacity. See also discussion in (Wiswede, et al., 2009).

Error related ERP components deviate in patients with disorders concerning emotional processing like depression or anxiety. Recent work further indicates that N_E modulation even occurs with variation of the personality trait anxiety in healthy individuals. Doreen Olvet and Greg Hajcak induced sad mood in healthy volunteers using hedonic film or music. Mood induction alone did not influence error processing in all participants, but

change in mood was related to N_E amplitude increase. That means that individuals who reported stronger mood induction after film or sound material (more sadness after film) showed larger N_E amplitude increases. Furthermore, volunteers rating high on neuroticism showed stronger mood and N_E effects (Olvet & Hajcak, 2011). As the authors state, this effect does not relate to a priori mood of the volunteers but to the ease it is influenced, and this is dependent on neuroticism.

To conclude, situations of failed cognitive control induce performance errors that come along with specific error related ERP components N_E and P_E, which have been located to cingulate and medial frontal cortex. Furthermore, error processing can be influenced by emotional manipulation, leading to the assumption that error processing might be vulnerable for impairment by olfactory stimulation.

5.4 INHIBITION, ERROR PROCESSING AND ETHANOL

The third substance examined in empirical *study IV* of this thesis was ethyl acetate for which neurotoxic effects have been shown, for example in animal models (Christoph, Hansen, & Leung, 2003). One ethyl acetate metabolite contributing to central nervous system impairment is ethanol. Subtle neurotoxic effects following alcohol ingestion have been examined in human volunteers and inhibition processes have been shown especially sensitive. Impaired response inhibition has been shown for example in a stop paradigm after ingestion of 0.62 g alcohol per kg body weight in healthy human volunteers causing blood alcohol concentrations of 50.2 mg/dl (Fillmore & Vogel-Sprott, 1999). Another investigation recorded ERPs in healthy human volunteers during performance of a go/nogo task after alcohol ingestion of 0.56 or 0.8 g/kg body leading to blood alcohol concentrations of 43 and 60 mg/dl respectively (Easdon, Izenberg, Armilio, Yu, & Alain, 2005). The authors reported consistent effects of both doses of alcohol consumption on behavior in form of increased error rate after ingestion, and on ERP measures in form of reduced amplitudes of the inhibition indicator *nogo-P3* and the error related *error negativity* N_E. Together these findings indicate that ethanol, which is

metabolized after ethyl acetate exposure, has the potency to impair inhibition and error processing.

Another interestingly aspect is that dis-inhibition disorders, like occurring during chronic alcoholism, has been compared to symptoms of attention deficit hyperactivity disorders (ADHD), which will be addressed in the discussion of *hypothesis III*.

6 EVENT RELATED POTENTIALS

Event related potentials (ERP) are a method to compute EEG recordings in order to analyze electric potentials derived from scalp surface electrodes in a stimulus related way. The method has been used since the 1960s with never ceasing intensity due to its exceptional good time resolution and its easy and cost-effective application. A nice introduction into the method, its advantages and disadvantages as well as a wealth of useful tips and tricks for planning and performing of EEG studies can be found in (S. J. Luck, 2005), which also served as main source for the following chapters.

For introduction and understanding of the concrete ERP components that were of relevance for the empirical study work, see chapter *5 Cognitive control and inhibition*.

6.1 METHODS AND SOURCES OF THE EEG

To record EEG in awake human volunteers, surface electrodes are attached to the scalp using a conductor gel in order to enhance signal transition from the scalp to the electrode. The signal that is recorded at the electrode originates from neural synaptic activity in the brain and more precisely from simultaneous activation of pyramidal neurons that are organized in parallel and aligned perpendicular to the scalp surface. The post synaptic potentials following excitation of pyramidal neurons cause depolarization at the synapse that comes along with counteracting hyperpolarization at the cell body. This difference in charge between synapse and cell body constitutes a dipole (one positive, one negative end). The signals from such single cell dipoles sum up throughout the brain, since it is a conducting medium, a phenomenon called volume conductance. The signal summation creates a single overall dipole at the scalp surface, where voltage differences at different locations can be recorded by a net of sensitive electrodes The potential difference between one active electrode, placed at a scalp region of interest, and one reference electrode, placed at a scalp region with minimal activity, provides the EEG signal in form of summed neural activation. The important features that have to be fulfilled for EEG recording are therefore a synchronous

activation of a sufficient amount of rectified pyramidal neurons in the right (perpendicular) position to the scalp surface.

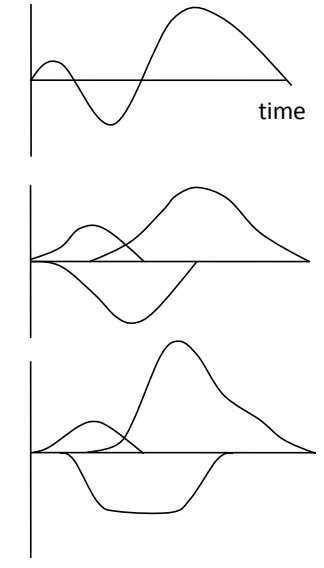

Figure 6.1: Schematic ERP (top) and possible sets of latent signals (middle, bottom) that would sum up to the same waveform (top). Derived from Luck (2005).

At this point of understanding, we have already touched a number of problems inherent to EEG recording. The first one is that we can only record synchronous activation of electrodes in the right alignment that evoke a signal that is strong enough. Furthermore, volume conductance delivers a summation of all concurrent neural activation, which causes the inverse problem. This means that from the activation pattern recorded at the scalp surface, we cannot easily infer the location of the generator of the recorded signal. In fact it is very likely, that what we measure as one potential difference at scalp level, is actually a sum of many simultaneous source activations (see *figure 6.1*). A range of solutions for this problem is currently in use, but will not further be touched in the current thesis. A third problem is inherent to the concept of a reference electrode. A point of no electrical activity is hard to find at the human body since a variety of other processes also generate electric signals, like for example muscular activation and the pulse. It therefore has to be assumed that such unrelated activity influences our data interpretation.

6.2 DATA QUALITY

The quality of the signal recorded at the electrode is severely impaired by transfer from the scalp to the electrode. Blurring is a common problem at this point of recording, which is reduced by inserting a conductive medium between electrodes and scalp

surface. The small size of the signal of interest (μV range) in contrast to the signal size of the disturbing signal (noise, mV) causes another problem. A traditional approach is the calculation of event related potentials, which I will describe in the next chapter.

The next source of data decay is the signal traveling through the cable connecting electrode and (analog-digital) signal converter. Despite cable isolation, it has traditionally been necessary to shield the EEG recording from electric fields, as for example generated from all sorts of power supplies, to avoid interference effects on the EEG signal that is traveling through the cable. For the current thesis work it was essential to counteract this effect in order to be able to record EEG in the non-shielded exposure chamber. A solution to this problem was given by active electrodes, which integrate a first signal amplifier already into the electrode (BioSemi, Amsterdam, The Netherlands). Furthermore signal transmission using optical fiber cables improved data quality. More background information can be found on the BioSemi homepage where relevant literature is listed (http://www.biosemi.com/products.htm).

6.3 CALCULATING EVENT RELATED POTENTIALS

As indicated in chapter 6.2 *Data quality*, the neural signal representing relevant brain activation is embedded in much stronger background noise. To get access to the signal of interest, event related potentials are calculated, taking advantage of the fact that irrelevant noise varies randomly over time and therefore adds up to zero, when averaged arbitrarily. Instead, neural responses that are related to a given event like the occurrence of a stimulus or a task should become enhanced by average building. ERPs are calculated by cutting the online EEG into segments that have a defined start like presentation of a sound. After repeated sound presentation, all sound-segments can be averaged over time, thereby representing neural activation that is specially related to the processing of the given event at time zero. By use of this technique, different deflections in the ERP (peaks and troughs) have been related to specific perceptual or cognitive processes, and theories about functionality and origin of these components have developed.

7 AIMS AND HYPOTHESES

The overall aim of the thesis was to investigate if chemosensory stimulation interferes with cognitive processes. To examine this, a number of methodological refinements, as compared to earlier investigations, were implemented in the study series. First, three substances with varying chemosensory potency were examined to assess the assumption that stronger chemosensory perceptions should cause stronger cognitive distraction. Second, a within-subject design was used to compare individual performances observed at three different exposure concentrations (low, middle, and high). Third, the cognitive task was selected based on current knowledge in the relevant fields of olfactory, cognitive and emotional processing. Fourth, EEG was implemented to extend the level of examination from behavioral to neural. The specific aims and hypotheses were:

Aim #1 was to examine if more intense chemosensory stimulation causes stronger cognitive distraction.

Aim #2 was to examine if more unpleasant chemosensory stimulation causes stronger cognitive distraction.

Aim #3 was to examine if unpleasant chemosensory stimulation shows comparable impairment on response inhibition as unpleasant visual stimulation.

Aim #4 was to examine if ERPs, derived from EEG recordings are more potent to detect a possible chemosensory distraction effect.

From these aims, specific hypotheses were derived which are introduced in the following.

Hypothesis I – Intensity: Higher chemosensory stimulation should evoke higher chemosensory effects in volunteers (objective, subjective level). Chemosensory distraction, as operationalized on the behavioral (reaction times, error rate) or neural level (ERP measures), should increase with increasing chemosensory effects (perception ratings).

Hypothesis II – Valence: Exposure to more unpleasant local irritants should evoke stronger emotional responses in volunteers. Increasing emotional responses, as operationalized by subjective annoyance ratings, should show a positive relationship to chemosensory distraction, as operationalized on the behavioral (reaction times, error rate) and neural level (ERP measures).

Hypothesis III – Inhibition: Stronger emotional responses, evoked by higher concentrations of unpleasant odors, should impair inhibition processes in the same way as has been shown for visual emotional contexts. In the flanker paradigm, the nogo-P3 amplitudes should be reduced during higher levels of unpleasant exposure.

Hypothesis IV – Error processing: The hedonic context that is evoked by unpleasant olfactory stimulation should influence error related ERP components and especially the N_E.

Hypothesis V – Neurotoxicity: Metabolism of the neurotoxic ethyl acetate increases ethanol blood alcohol levels. Impairment of inhibition and/or error processing mechanisms might occur as earliest subtle indicator of neurotoxicity as an result of ethyl acetate exposure.

8 METHODS

Current investigations aimed to elucidate if cognitive impairment effects that were reported in earlier studies could be found in the general population of healthy human volunteers (C van Thriel, et al., 2003; C van Thriel, et al., 2007) with help of a whole-body exposure laboratory (*figure 8.1*) and electrophysiological measurements, which deliver data on the neural level in order to identify earliest impact of acute, short-term inhalation of neurotoxic substances.

Figure 8.1: Picture of human volunteers in the exposure laboratory used in all studies.

A highly controlled exposure design comparable to earlier studies (C van Thriel, et al., 2003; C van Thriel, et al., 2007) was implemented in all three studies contributing to the current thesis. To examine *hypotheses I* and *II*, cyclohexylamine and propionic acid were selected since it was expected from earlier studies that cyclohexylamine should show stronger chemosensory effects at exposure levels below OEL values (C. van Thriel et al., 2006). Ethyl acetate instead was selected due to its neurotoxic potency. Of special interest was the possibility to formulate specific hypotheses due to the assumed neurotoxic effects mediated via the ethyl acetate metabolite ethanol (*Hypothesis V*).

8.1 INHALATION EXPOSURE

Whole-body, four-hour inhalation exposure at concentrations derived from current OEL values were chosen in order to relate study results to workplace conditions. Schematic draft of exposure concentrations, representative for all three studies is given in *figure 8.2*. Repeated data collection during four-hour exposure allowed for examination of time-related effects like olfactory mediated adaptation versus trigeminal mediated sensitization and exposure unrelated tiredness effects. The balanced within-subject design, using three exposure concentrations ranging between odor thresholds and OEL

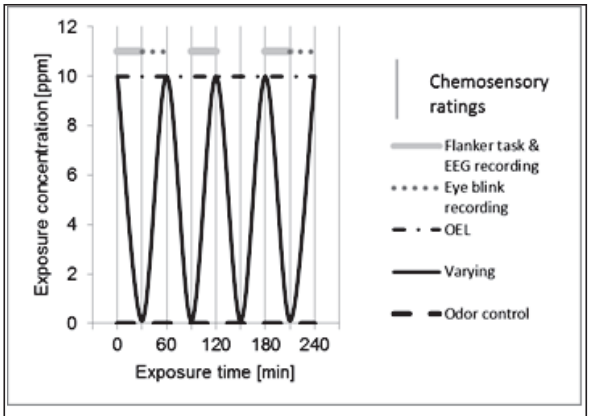

Figure 8.2: Exemplary scheme of exposure designs as implemented to all three studies.

values including one varying condition for each substance, allowed for examination of a dose-response relationship and effect amplification during exposure peaks. Participants of the study were healthy male, non-smoking volunteers who reported no special sensitivity towards chemosensory stimulation.

8.2 CHEMOSENSORY EFFECTS

Chemosensory effects were collected repeatedly on the objective and subjective level to operationalize exposure related chemosensory intensities and their hedonic valence (see *hypothesis I* and *II*). Subjective ratings were collected before and after each exposure as well as nine times during each four-hour session. We used the Labeled Magnitude Scale (LMS), as developed by Green and colleagues (Green et al., 1996), as well as the modified chemosensory symptoms subscale derived from the Swedish Performance Evaluation System (SPES), which was developed by Iregren and colleagues (Iregren, Gamberale, & Kjellberg, 1996). Ten of the eleven ratings collected by LMS served as intensity measure for chemosensory effects. The eleventh LMS perception of *annoyance* has been shown influenced by hedonic stimulus valence (P. H. Dalton, Dilks, & Banton, 2000; Lindvall & Radford, 1973) and was therefore used as indicator for evoked hedonic valence, together with the SPES dimension 'olfactory symptoms' comprising the items *bad air*, *nasty smell*, *unpleasant smell*, *stink*.

8.3 FLANKER TASK

To approach *Hypotheses III*, *IV* and *V* a hybrid go/nogo flanker task, which is outlined in figure 8.2, was performed by the volunteers three times during each exposure.

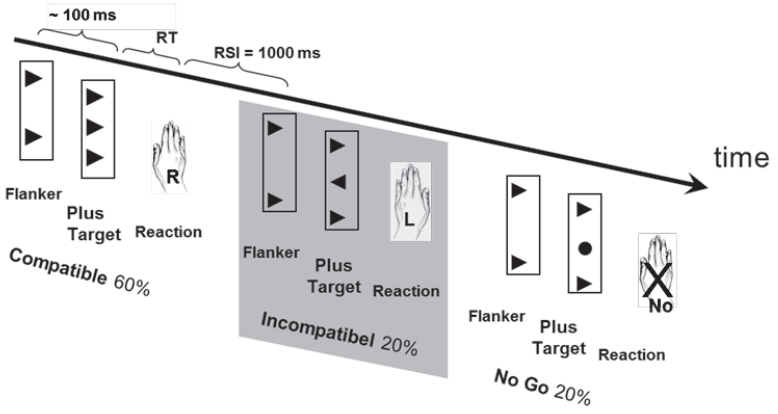

Figure 8.2: Time-flow of flanker task. Facilitating flanker occurred 100 ms before target stimulus, indicating which hand to respond with. Flanker stimuli were predictive in 60 % of cases (compatible). In 20 % of cases, responses had to be given with the contradictory hand (incompatible) and in 20 % of cases the initiated response tendency had to be completely inhibited (nogo).

The go/nogo flanker task allows to compare conditions of automatic motor execution (compatible go trials) with conditions of complete motor inhibition (nogo trials) and conditions involving the processes of response conflict, -selection, -inhibition and -initiation (incompatible go trials). In addition, it has been shown earlier that incompatible as compared to compatible trials impair performance accuracy sufficiently to allow for analysis of processes involved in performance monitoring.

9 RESULTS AND DISCUSSION

In the following I will present results from the studies in relation to the hypotheses formulated in *chapter 7*.

9.1 HYPOTHESES I AND II: INTENSITY VERSUS VALENCE

To compare perception intensities evoked by propionic acid and cyclohexylamine exposure, rating profiles collected by labeled magnitude scale are given in *figure 9.1*.

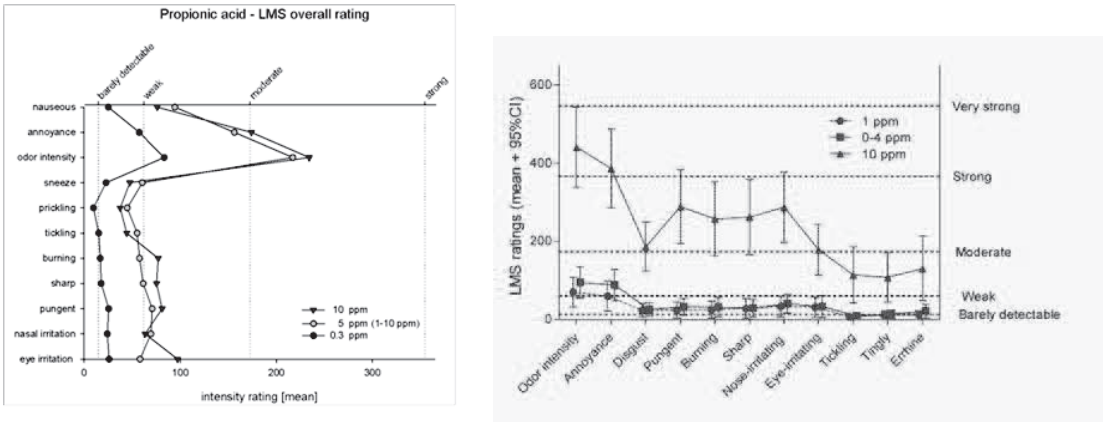

Figure 9.1: Profile of labeled magnitude scale (LMS) intensity ratings as collected during three four-hour inhalation exposures for each substance are given. Propionic acid (23 participants) is given to the left and cyclohexylamine (24 participants) to the right. Mean values (participants, 9 time points) are given for three olfactory (odor intensity, annoyance, disgust) and eight trigeminal mediated perceptions. Figures correspond to *fig 1* and *fig 2* from *study I* and *II* respectively.

These mean ratings confirmed the prediction derived from an earlier publication (C van Thriel, et al., 2007) that high, constant cyclohexylamine exposure (10 ppm) evoked stronger chemosensory intensity ratings than high, constant propionic acid exposure (10 ppm). This was overall true for ratings of chemosensory perceptions and especially for annoyance ratings, which reached the level of *moderate* during propionic acid exposure and the level of *strong* during cyclohexylamine exposure. The same was true for collected SPES ratings, where acute olfactory symptoms during propionic acid were

rated below *somewhat*, as compared to ratings above *rather much* during cyclohexylamine exposure[5]. Corresponding SPES results can be found in *fig 3* from *study I* and *fig 4* from *study II*.

The main predictions in *hypotheses I* and *II* were that chemosensory distraction should increase with perceived stimulus intensity and hedonic valence. Despite higher values for both perception ranges during cyclohexylamine exposure, impaired neurobehavioral performance occurred during propionic acid exposure only (*figure 9.2*).

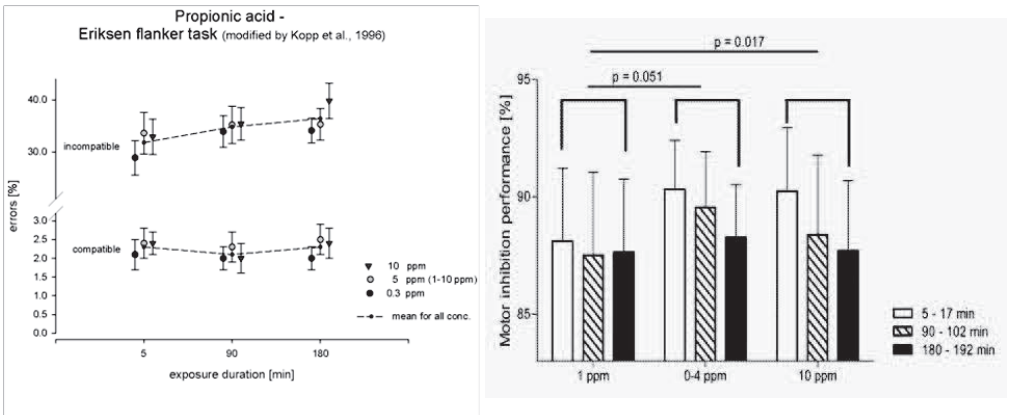

Figure 9.2: Performance in flanker task during propionic acid (left, error rate) and cyclohexylamine exposure (right, correct responses) are given for three exposure concentrations at three time points. Significant main effect of concentration during propionic acid exposure is shown in mean and standard deviations (23 participants) for compatible and incompatible flanker conditions (left). Time X Concentration interaction during cyclohexylamine exposure is shown in mean (24 participants) and 95% confidence intervals (right). Figures correspond to fig 5 and fig 6 from study I and study II respectively.

Figure 9.2 shows that propionic acid mean error rates at varying and high exposures lied above those at odor control condition. The especially strong error increase at the end of constant high (10 ppm) exposure indicates that chemosensory sensitization rather than adaptation evolves during exposure. Cyclohexylamine performance accuracy was lowest

[5] The swedish performance evaluation system (SPES) has the form of a Likert scale ranging from *not at all*, *hardly*, *somewhat*, *rather much*, *considerably*, to *very very much*.

during odor control condition, as compared to better performance at both varying and constant high exposures. These chemosensory distraction results cannot be aligned with the assumption of a simple, linear dose-response relationship that considers only odor intensity and the strength of the evoked emotional response (annoyance). It was speculated that special characteristics immanent to olfactory processing underlie these findings. One assumption is that other substance features (in addition to intensity and hedonic tone) contribute to interference of chemosensory stimulation with concurrent cognitive performances[6].

Until now, only two dimensions of odorant perceptions were considered: intensity and hedonic valence. However, the odor percept can be described in more detail, for example by use of odor quality classification schemes (Dravnieks, 1982). An interesting fact is that the odor percept seems to be a rather fragile construct, which is influenced by many factors. Repeated exposures have been shown to increase perceived familiarity which in consequence comes along with stronger intensity and pleasantness ratings. For exhaustive overview, see chapter four of (Wilson & Stevenson, 2006). Instead of being related to odorant intensity and/or hedonic valence alone, chemosensory distraction might be related to a more complicated interaction pattern of intensity, hedonic valence, familiarity and overall odor quality. To systematically examine the influence of such odorant characteristics might help clarify the existing open questions.

Another interesting characteristic that might influence the odor percept, which in turn could modify chemosensory mediated distraction, is related to the *Mnemonic Theory of Odor Perception* (Stevenson & Boakes, 2003). In this paper the authors report evidence that hedonic responses to odorants are not innate (as they are for taste) but instead are acquired during very effective association learning mechanisms. In an early study, olfactory association learning has been claimed to be especially fast, long lasting (Lawless & Engen, 1977) and automatic (Kirk-Smith, van Toller, & Dodd, 1983). The *Mnemonic Theory of Odor Perception* assumes that odor objects are automatically saved

[6] The possibility of especially potent distraction following subliminal chemosensory stimulation has been discussed in study II but does not hold when comparing results of study I and II.

as engrams in a memory store. This odor encoding is influenced by input from other modalities making the odor engram multi-modal. The authors argue that such multimodality provides for the fast and automatic association learning observed in olfaction learning. In a later neuroanatomical extension of the same model, Wilson and colleagues identified the piriform cortex as potential memory store. The broad multimodal connectivity, including amygdala, supported the multimodality assumption of odor engrams (Wilson & Sullivan, 2011).

In the context of our results, such odor object learning would indicate that each individual develops a unique odor object representation that is strongly influenced by the individual's exposure history but also other, multimodal context effects. Depending on context and hedonic state (mood) during first odor encounter, different odor engrams will be generated in each individual with individually varying impact on concurrent cognitive task performance. In the discussion of *study II*, I name further factors promoting an increased inter-individual variability in chemosensory responsiveness (D. Shusterman, 2002) like personality traits (Chen & Dalton, 2005), cognitive bias (P. Dalton, 1996, 1999) or the influence of cognitive abilities (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010).

9.2 *HYPOTHESES III AND V: INHIBITION AND NEUROTOXICITY*

Addressing performance in nogo flanker trials allows for isolation of response inhibition. Incompatible trials require additionally solving of the conflict between contradictory response tendencies evoked by flanker and target stimuli. Comparison of performance and ERP measures between nogo and incompatible trials therefore may help interpretation of results. On the neurobehavioral level, accuracy was collected as amount of errors. Reaction times showed very little variation due to the highly automatic character of the flanker task (*chapter 8*). On the electrophysiological level, ERPs were calculated following target stimulus presentation, which represent the condition of complete motor inhibition in nogo trials and the combined activation of conflict processing and inhibition in incompatible trials. Both conditions of conflict and response inhibition evoke N2 and P3 components and peak amplitudes and latencies

were therefore analyzed in the respective time ranges (*Studies III* and *IV*). Data (error rate, ERP peak amplitude and latency) were analyzed using repeated measurements ANOVA including the factors *Concentration* (odor control, varying, OEL), *Time* (beginning, middle, end), *Compatibility* (compatible, incompatible, nogo) and *Electrode* position (ERP measure).

9.2.1 Behavioral results

Behavioral data are given in *figure 9.2*. Repeated measurements ANOVA did not show special exposure related impairment for incompatible or nogo trials. Detailed data are given in *table 9.1* for ***A*** cyclohexylamine, ***B*** ethyl acetate and ***C*** propionic acid. *Study I* reported an overall main effect of rising exposure concentration on increasing performance errors (see *figure 9.2*). Although this effect showed no interaction for *compatibility* and was therefore not specific for incompatible or nogo trials, it can be seen from *table 9.1C* that error rate increased exposure related for incompatible (29% to 29% to 33.7%) and nogo trials (12.9% to 14.7% to 16.3%) but not for compatible trials (3.2% to 3.9% to 3.6%). Results were comparable for EEG group and non-EEG group. For exposure to ethyl acetate, repeated measures ANOVA revealed a *concentration* X *time* interaction that was explained by significant error increase during odor control condition (3 ppm) but not during higher exposures. It can be concluded that no indication for an early neurotoxic effect of ethyl acetate exposure could be found on the behavioral level.

The controlled exposure design with four-hour whole-body exposure to increasing substance concentrations in a within-subject design could not show the predicted specific behavioral impairment of response inhibition or conflict processing. A trend for elevated error rates with increasing exposure concentration was however found for propionic acid exposure. ERP results will be examined next, since it is not uncommon that experimental effects occur on the neural but not on the behavioral level.

Table 9.1: Task performance in go/no-go flanker task, mean (3 time points) and standard deviations (SD) comparing EEG (6) and non-EEG group (18) for ***A*** cyclohexylamine, ***B*** ethyl acetate and ***C*** propionic acid exposure

A	***Cyclohexylamine***					
	1 ppm		*0 – 4 ppm*		*10 ppm*	
	Non-EEG	*EEG*	*Non-EEG*	*EEG*	*Non-EEG*	*Non-EEG*
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
Correct (%)						
All	91.6 (5.4)	93 (2.8)	92.9 (3.8)	92.7 (2.8)	92.6 (4.9)	92.3 (3.9)
Compatible	98.1 (1.4)	98.6 (0.9)	98 (2.1)	98.3 (0.7)	98.3 (1.8)	98.1 (1.4)
Incompatible	73.4 (14.8)	78.3 (7.5)	77.9 (11.2)	77 (8.9)	76.9 (13.9)	76.2 (12.9)
No-go	90.1 (12.4)	90.8 (5.8)	92.8 (6.4)	91.3 (5.5)	91.4 (9.7)	91.1 (6.2)
Reaction time						
Compatible	257.4 (33.8)	252.3 (31)	261.8 (31.4)	250.4 (32.9)	261.6 (29.2)	251.6 (29.4)
Incompatible	344.7 (34.3)	320.5 (43.3)	347.5 (34.3)	318.8 (50.4)	345.4 (33.6)	322.5 (44.8)

B	***Ethyl acetate***					
	3 ppm		*400 ppm*		*0 – 800 ppm*	
	Non-EEG	*EEG*	*Non-EEG*	*EEG*	*Non-EEG*	*EEG*
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
Correct (%)						
All	93.6 (4)	91.6 (4.8)	93.8 (4.6)	92.7 (3.6)	94.3 (3.7)	92.1 (4.6)
Compatible	98.3 (2.1)	98.2 (1.2)	98.4 (2.8)	98.7 (1)	98.7 (1.3)	98.2 (1.1)
Incompatible	79.6 (13.3)	75.1 (13.8)	80.4 (13.8)	76.5 (10.6)	81.7 (12)	76.7 (13.5)
No-go	93.7 (5.2)	87.8 (9.1)	93.3 (8)	90.9 (5.6)	93.9 (5.3)	89 (10.3)
Reaction time						
Compatible	258.6 (25.8)	246.9 (25.1)	261.3 (31.4)	246.8 (22.1)	261.9 (28.3)	245.2 (33.5)
Incompatible	337.5 (31.8)	345.8 (40.8)	342.7 (39.2)	343.4 (38.5)	340.8 (34.9)	331.6 (54.3)

C	***Propionic acid***							
	0.3 ppm		*0 – 10 ppm*				*10 ppm*	
	Non-EEG	*EEG*	*Non-EEG*		*EEG*		*Non-EEG*	*EEG*
	Mean (SD)	*Mean (SD)*	*Mean*	*SD*	*Mean*	*SD*	*Mean SD*	*Mean SD*
Error Rate [%]								
Compatible	1.7 (1.4)	3.2 (1.8)	1.9 (1.5)		3.9 (2.4)		1.9 (1.3)	3.6 (2.2)
Incompatible	33.1 (15.2)	29.0 (9.5)	36.4 (18.0)		29.0 (11.2)		36.7 (17.0)	33.7 (11.5)
NoGo	18.2 (17.9)	12.9 (8.2)	20.5 (19.2)		14.7 (8.3)		20.9 (17.6)	16.3 (8.0)
Reaction Time [ms]								
Compatible	230 (28.8)	243.7 (24.2)	226.0 (31.2)		243.6 (26.1)		228.1 (29.4)	238.5 (24.9)
Incompatible	306.7 (36.6)	316.9 (18.2)	302.2 (36.2)		316.4 (21.2)		306.9 (36.7)	315.5 (29.2)

9.2.2 ERP results

Results from ERP recording are given in *figure 9.3*. Grand average ERPs are shown from ***A*** compatible, ***B*** incompatible and ***C*** nogo trials during exposure to odor control, varying and OEL concentrations (within each diagram) for cyclohexylamine (top), propinic acid (middle) and ethyl acetate (bottom) exposures. Grand averages were calculated, including six participants and recordings at three time points. More details are given in studies III and IV. In general, the waveforms display typical patterns as expected from go/nogo flanker tasks, thereby indicating successful method implementation. ERP peaks representing N2 and P3 components can be seen, although to a varying degree with somewhat more distinct N2 peaks in cyclohexylamine and ethyl acetate exposures and broader but smaller deflections during propionic acid exposure.

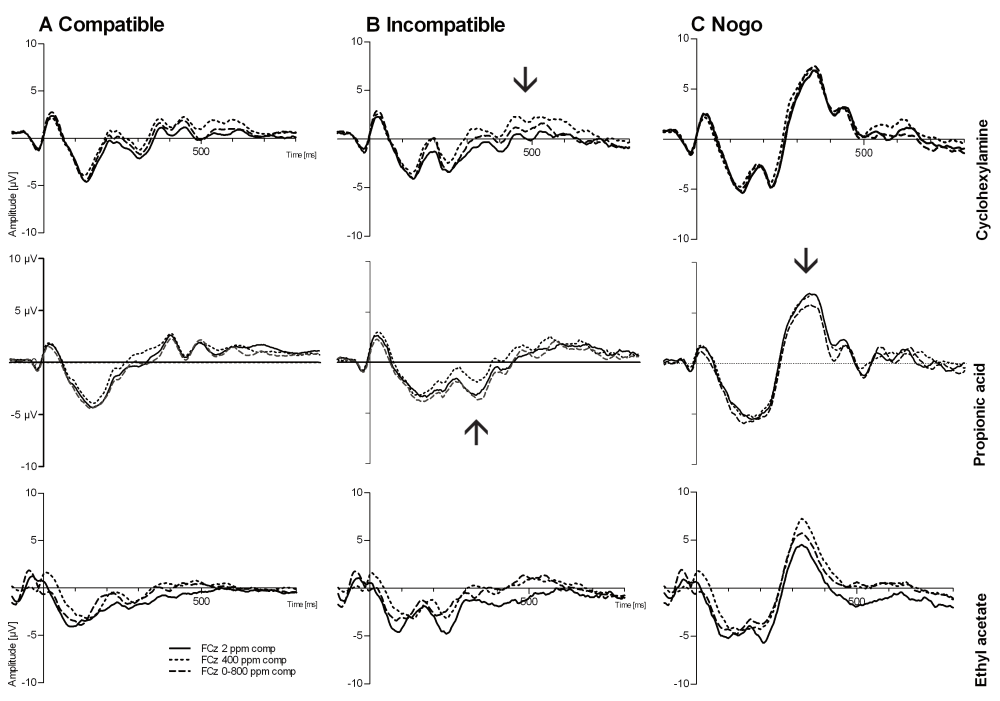

Figure 9.3: Stimulus-locked ERPs (grand averages of 6 volunteers at 3 time points) at fronto-central electrode FCz from correct ***A*** compatible, ***B*** incompatible and ***C*** nogo conditions during three exposures to cyclohexylamine (top row), propionic acid (middle row) and ethyl acetate (bottom row).

Exposure related effects within substances occur only weakly. As a common trend across all substances appears a concentration related modulation in the N2 time range of incompatible trials in a way that ERP curve at that time is shifted to positive during varying exposures (but not during highest exposures). In nogo trials no common exposure related pattern occurs.

9.2.2.1 Inhibition – the nogo conditions

ERP results from nogo conditions give an ambiguous picture: no exposure effect on nogo-P3 was found in cyclohexylamine exposure, a reduction of nogo-P3 occurred during propionic acid exposure, and nogo-P3 (on a descriptive level) increased during ethyl acetate exposure. The significant reduction of nogo-P3 amplitude during propionic acid exposure (OEL) corresponded to reduced accuracy on the behavioral level, as described in the section on behavioral data.

As discussed in *study III*, nogo-P3 reduction during unpleasant propionic acid exposure corresponded well with literature from visual emotion research, which was summarized in chapter *5 Cognitive control and inhibition*. Propionic acid results thereby fit to the interpretation that inhibition processes can be impaired by an unpleasant emotional context, whereas positive context has earlier been shown to enhance inhibition (Albert, et al., 2010; Albert, et al., 2012), as represented in reduced and increased nogo-P3 amplitudes. Support has been given on the visual modality and comparable findings are reported from olfactory evoked contexts (Kato, et al., 2012).

Recently, (Wild-Wall, Oades, Schmidt-Wessels, Christiansen, & Falkenstein, 2009) and colleagues reported a comparable reduction of the nogo-P3 amplitude in children suffering from attention deficit syndrome (ADHD). At this background it could be speculated that unpleasant and potentially dangerous background stimulation might activate the olfactory warning system, as described in *chapter 2*. In consequence, background monitoring processes might be initiated, putting our volunteers in an ADHD-like state. To confirm this speculation, further cognitive processes that have been shown to be impaired in ADHD patients could be examined during chemosensory exposures.

A strong drawback for *hypothesis III* however remains, since ERP effects of nogo-P3 reduction did not show clear relationship to emotional evaluation of the background exposure. Whereas within-substance analysis for propionic acid exposure showed the expected dose-response relationship of impaired inhibition during highest and most annoying exposure concentration, this pattern was not given during exposure to the stronger annoying cyclohexylamine. As discussed in hypothesis I and II, cyclohexylamine exposure expressed higher ratings of odor intensity and annoyance but this stronger emotional background did not have a stronger impact on response inhibition. Since we will see that this problem is also relevant for the next hypothesis IV, it will be addressed in the final chapter *10 Overall discussion*.

9.2.2.2 Including conflict – the incompatible conditions

As stated in the introductory part of this chapter, exposure concentration modulated negative deflections in the N2 time-range uniformly for all three substances, showing clear positive shifts in the waveforms recorded during variable exposures. This effect was strongest during cyclohexylamine exposure, weaker for propionic acid, and did not turn significant at ethyl acetate exposure, despite the apparent effects in the grand averages in *figure 9.3*. Repeated measurement ANOVA revealed significant main effect of concentration for cyclohexylamine exposure on all amplitudes of P2, N2, and P3a peaks. For propionic acid data, the same analysis showed significant effects only at peak deflection N2, which is shown in the bar diagram in *figure 9.4*. For detailed statistical outcome see result sections of *studies III* and *IV*.

These results followed the prediction that exposure to local irritants that evoke stronger chemosensory effects (cyhexylamine) should show stronger cognitive effects. However, this effect occurred during variable exposure that reached lower time-weighted average exposure levels than constant high OEL exposures, which was 2 ppm for cyclohexylamine and 5 ppm for propionic acid, as compared to 10 ppm during OEL conditions for both substances.

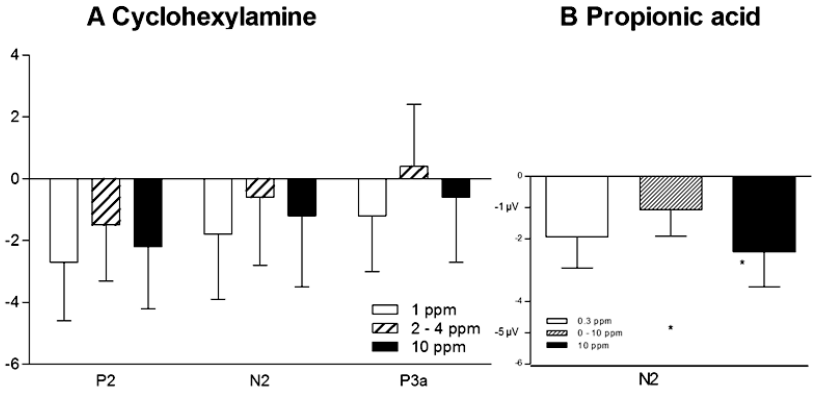

Figure 9.4: Target-locked ERP data from go/nogo flanker task during **A** cyclohexylamine and **B** propionic acid exposure. Mean amplitudes (6 subjects, 3 time points) and standard error (SE) of amplitudes at electrode FCz are given from correct incompatible trials. All amplitude reductions during varying exposure were statistically significant.

These lower exposure levels evoked correspondingly lower chemosensory effects, as shown in *hypotheses I* and *II* or result section of *studies I* and *II*. Instead of absolute intensity of the perception, the variable character of stimulation seems to be essential. Theoretically it is reasonable to assume that a varying stimulation of potential danger requires a constant monitoring process since the changing situation has to be evaluated continuously and thus no final conclusion regarding safety or danger can be drawn.

In conclusion, some special characteristics of variable exposures seem to interfere especially with the cognitive control mechanisms executed during incompatible conditions, but not during pure motor inhibition, as required in nogo trials. Interpretation of this effect is difficult, as already indicated in discussion of *study IV*, because of the extendedness of this effect over P2 – N2 peaks during propionic acid exposure, and even extending to P3a peak in cyclohexylamine exposure. From the curve pattern it looks like an additional underlying component provides the whole curve with a positive shift during variable exposure. The nature of this component /shift however is not clear and no comparable effects have been found in the literature.

9.2.2.3 Neurotoxicity

Neurotoxic substance effects are often described only on an unspecific level as overall sedation of the CNS, which can be explained by the fact that they are examined in the animal model where critical endpoints often are overall effects like reduced locomotion or increased arousal. In contrast, alcohol intoxication in humans is well examined due to the high voluntary self-exposure and the consequences for the health care systems. Impaired inhibition has been identified as one well described and specific neurotoxic effect after alcohol ingestion. In consequence we examined nogo trials for a dose-response effect of ethyl acetate exposure.

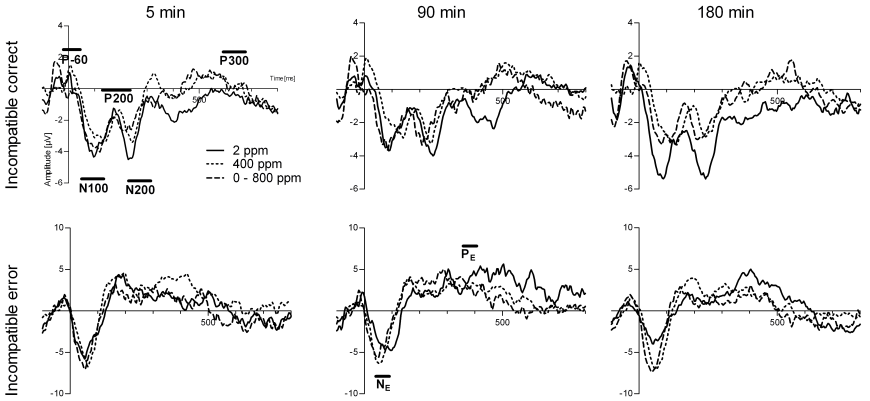

Figure 9.5: Grand averages from target-locked ERPs of correct incompatible trials (upper row) and response-locked ERPs of erroneous incompatible trials during the go/nogo flanker task at beginning, middle and end of exposure to ethyl acetate.

Grand average ERPs showed a range of curve changes during higher exposure concentrations. However, none of the differences were significant in the repeated measurement ANOVA and these descriptive effects are therefore hard to interpret, as was already stated in the discussion of *study IV*. The most interesting effects seemed to be the reduction of N_E amplitude during lowest ethyl acetate exposure, since it was enhanced with duration of four-hour exposure, as can be seen in *figure 9.5* and since it was in agreement with neurobehavioral effects as reported earlier.

However, this effect was contradictory to earlier findings following moderate levels of alcohol consumption (Easdon, et al., 2005), and was only present during lowest ethyl

acetate exposure. It can therefore not be interpreted as a neurotoxic effect. ERPs from incompatible trials are also given in *figure 9.5*. The non-significant N1 and N2 amplitude reductions indicate development over time which would be expected for a neurotoxic effect, due to substance accumulation over time. However, again interpretation of this effect is currently not possible since too many elements of uncertainty are present in the data. The small study group size, the large inter-individual variability (see results *study IV*) the lack of significance and the contradiction to the formulated hypotheses (*chapter 7*). It would be interesting to repeat the same investigation in a larger study group for better understanding of the results.

9.3 *HYPOTHESIS IV: ERROR PROCESSING*

As expected, the well-known compatibility effect was evoked in the flanker task in form of reduced accuracy (error rate) and response speed (reaction times) in incompatible as compared to compatible trials. Error rate was high enough to analyze the resulting response related ERPs following erroneous responses in incompatible trials (Olvet & Hajcak, 2009). See table 9.1 for detailed error rates. However, as discussed earlier, error rate was not influenced by exposure intensity and hedonic tone as expected. The same discussion as given in context of *hypothesis I* holds true also for the current chapter.

Response-locked grand average ERPs from erroneous incompatible trials are given in *figure 9.6.* Nice and characteristic error-waves can be seen despite small group size. Some variation occurs as to amplitude of N_E related peak. This could for example be explained by the slightly higher rate of performance errors in EEG group during propionic exposure, which ranged between 29 – 33 % as compared to cyclohexylamine 22 – 24 % and ethyl acetate exposure 24 – 25 %.

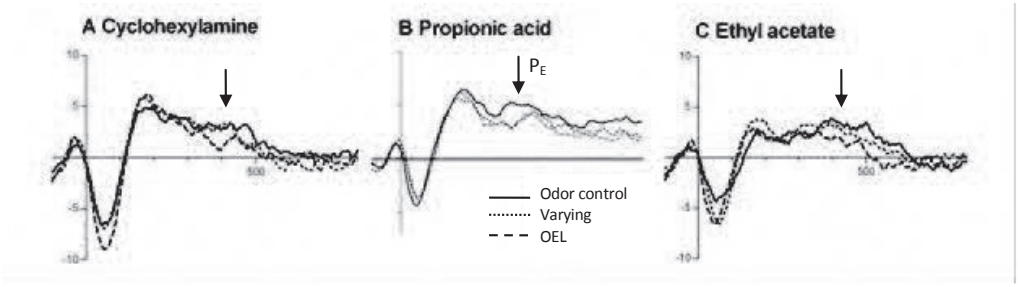

Figure 9.6: Response-locked ERPs (grand averages of 6 volunteers at 3 time points) at fronto-central electrode FCz from erroneous incompatible trials during three exposures to ***A*** cyclohexylamine, ***B*** propionic acid ***C*** ethyl acetate. OEL: Occupational exposure limit.

The only significant effect was an amplitude reduction in the P_E during variable exposure to propionic acid. None of the two earlier studies that integrated (visual) emotional background stimulation to flanker task performance reported effects on P_E related peaks, but visual inspection of grand averages given by Wiswede and colleagues indicate a trend into the same direction, reduced P_E amplitude following unpleasant pictures

(Wiswede, et al., 2009). Looking at grand averages from cyclohexylamine and ethyl acetate exposure, shows somewhat related curve trends with a negative shift of the ERP curve in error-related ERPs at 400 ms. Such concordant trends on P_E amplitude in propionic acid, cyclohexylamine and ethyl acetate exposure might indicate an underlying effect that could not be detected in the current analyses, due to the small sample size. Another (non-significant) trend in error-related ERPs from cyclohexylamine and ethyl acetate exposure (but not propionic acid), are enhanced N_E amplitudes. Indeed, N_E enhancement in an unpleasant (visual) context was reported by Wiswede and colleagues (Wiswede, et al., 2009).

10 OVERALL DISCUSSION

The empirical studies underlying the current thesis used a carefully planned and well-balanced study design, which earlier provided valuable evidence for or against existence of acute neurobehavioral or chemosensory effects during low-level whole body inhalation exposures below OEL levels (C van Thriel, et al., 2003; C van Thriel, et al., 2007; Christoph van Thriel et al., 2005). The substances used in studies I, II, and III were pre-evaluated regarding their chemosensory effects in human volunteers (C. van Thriel, et al., 2006). The subjective perception ratings, confirmed both a-priori expectations that higher concentrations of one substance should evoke higher ratings, and that the more chemosensory potent cyclohexylamine should evoke hither ratings than moderate propionic acid. Chemosensory results were therefore regarded as of high reliability and validity.

Predictions derived from aim #1 and aim #2 could not be confirmed. It was not possible to predict neurobehavioral effects based on perceived stimulus intensity and hedonic valence. Instead, only propionic acid that evoked intermediate chemosensory perceptions showed dose related neurobehavioral (error increase) and electrophysiological impairment (reduced nogo-P3).

The assumed evolutionary relevance of an olfactory warning system together with findings that indicated special interference between emotional context and inhibition mechanism led to the assumption that response inhibition should be an especially vulnerable function. By extending the analysis from the neurobehavioral to the electrophysiological level it was expected to reach better understanding of the proposed olfactory interference effect. The absence of effect could be due to a number of reasons.

For the first, interference effect between emotional context and inhibition processes were mainly reported within the visual modality in the past. There was only one exception in form of the study by Kato and colleagues as discussed in *chapter 5*. It is therefore possible that the proposed interference only occurs for the visual modality, or that it is not present in cross-modal settings like examined in the current studies.

Second, the stereotype-like characteristics of the flanker task might not have been challenging enough. Another task using conflicting information on the level of emotional processing might have been more appropriate. To test this possibility, a comparable inhibition task evoking an emotional conflict between the background chemosensory exposure and the inhibition task should be tested. For example, chemosensory and visual stimuli could be categorized on the valence dimension (un/pleasant) and paired in all possible combinations (pleasant-pleasant, pleasant-unpleasant, etc.) in a go/nogo task. Such a design would help to understand if emotional conflict is necessary to evoke the reported emotion-inhibition interference.

Actually, only the two studies performed by Albert and colleagues used target material without hedonic valence (letters) on an emotional background (Albert, et al., 2010; Albert, et al., 2012; Goldstein, et al., 2007). The other three studies used hedonic target stimuli (words like happy, angry) on emotional backgrounds (emotional faces). The tasks did not focus on the hedonic content (respond to *italic* words). More information on these studies were given in *chapter 5* (Egner, et al., 2008; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Goldstein, et al., 2007).

A third factor of relevance may relate to the specific characteristics reported for olfaction. Some points that have been reported earlier (*study II*) will only be mentioned shortly now. First, high inter-individual variance in chemosensation might have weakened a possible effect (D. Shusterman, 2002). Second, cognitive bias has been shown to modulate evaluation of chemosensory perceptions and in consequence, safety affirmations given in advance of the study might have reduced evaluation of the emotional impact of the exposure (P. Dalton, 1996, 1999). Third, other odor characteristics like familiarity and quality might have blurred potential effects. Fourth, inhalation exposure studies might in general only attract individuals that are less influenced by chemosensory stimulation. Finally, following the *Mnemonic theory of odor perception*, given in *chapter 2*, individual exposure history and current mood at first odorant encounter may have diversified the individual odor objects, which in turn have diverging effects on the volunteers (Stevenson & Boakes, 2003).

Another inter-individual factor that has not been discussed yet is differences in cognitive skills, as recently reported by Hedner and colleagues (Hedner, et al., 2010). The authors show that proficiency in executive functioning and semantic memory improved performance in cognitive odorant processing like odor discrimination and identification. Related to this topic is the earlier finding from van Thriel and colleagues, who showed that high performance in odor discrimination was associated with lower ratings of odor intensity (Christoph van Thriel et al., 2008). This finding reminds of our ability to cognitively control emotional processes. To attend emotional stimulus features, instead of passive viewing, has been reported to reduce amygdala activation and thereby the emotional impact of the affective stimulus (reviewed by (Ochsner & Gross, 2005). Comparably, the attended, cognitive evaluation of the chemosensory stimulation, given via LMS and SPES during exposure, might have reduced the emotional impact of the exposure. This effect would be comparable to the affective labeling theory (Lieberman et al., 2007).

In conclusion, introduction of ERP techniques has been shown feasible in the current exposure studies. The method is easy to apply, delivers high time resolution, and information from neural level responding. ERPs from incompatible trials that showed special sensitivity for variable chemosensory exposure condition indicate the exciting possibility that it is not the exposure intensity per se that has the strongest impact on concurrent cognitive performance, but that it is a changing environment that poses the strongest distraction potential. This hypothesis could be investigated not only in the chemosensory modality but in easier addressable modalities like vision or audition.

It was not possible to confirm the initial hypotheses and the question if chemosensory stimulation is a source for cognitive interference and if it thereby poses a risk at workplace can still not be answered.

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